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TULAREMIA

THE MICROSCOPIC CHANGES OF THE LESIONS IN MAN

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During 1924, 1925 and 1926, the number of states of the United States in which cases of tularemia in human beings were recognized increased from six to thirty-four, and the number of case reports increased from fifteen to three hundred and twenty-three; in addition, the identity of "Ohara's Disease" occurring in Japan, and tularemia occurring in the United States, was demonstrated. This indicates that physicians have learned to recognize a disease which has doubtless passed unrecognized for years.

The great reservoir of infection is wild rabbits.

The principal modes of transmission to man are: (1) by the bite of the horse fly, *Chrysops discalis;* (2) by the bite of the wood tick *Dermacentor andersoni* Stiles; (3) by contamination or self-inoculation of one's hands or conjunctival sac with portions of the internal organs or the body fluids of infected rabbits, flies or ticks.

In studying 323 case reports, four clinical types are noted: (1) ulceroglandular, the primary lesion being a papule, later an ulcer of the skin, accompanied by enlargement of the regional lymph nodes; (2) oculoglandular, the primary lesion being a conjunctivitis, accompanied by enlargement of the regional lymph nodes; (3) glandular, without a primary lesion but with enlargement of the regional lymph nodes; (4) typhoidal, without primary lesion and without glandular enlargements.

The various phases of tularemia have already received full discussion in the literature, with the exception of the pathologic condition in man. It is therefore the purpose of this paper to present the microscopic changes of the lesions in man, making reference to the animal pathology for comparison.

Subacuteness approaching chronicity characterizes the lesions in man. This applies to the primary ulcer at the site of infection, the regional lymph nodes which drain the site of infection, the subcutaneous nodules

in the course of the lymphatics lying between the ulcer and the nodes and the internal organs—spleen, liver, lungs, lymph glands and suprarenals.

Infection of maximum virulence meets resistance and immunity in man, but in susceptible laboratory animals—guinea-pig, rabbit and white mouse—it encounters little or no resistance; there is, therefore, a marked contrast between the human and the animal lesions.

The granulomatous type of the human lesions corresponds to the subacute clinical course manifested by the disease in man.

Pathologists, unfamiliar with the lesions in man, have tenaciously clung to the diagnosis of tuberculosis until forced to give it up by their failure to demonstrate acid-fast micro-organisms or to infect guinea-pigs. In such cases, the rabbit history and serum agglutination have proved the diagnosis of tularemia. *Bacterium tularense* has not been stained in sections of human lesions.

The material which formed the basis for the present study was received at the Hygienic Laboratory of the United States Public Health Service from physicians in the form of gross specimens, stained and unstained sections, blood serum for the agglutination test in each case and carefully prepared case notes.

Necropsies were performed in cases 1, 2 and 3. Verbrycke [1] reported one, Francis [2] observed a partial necropsy and Bruecken [3] generously placed at our disposal a complete unpublished autopsy report which he made in case 1, together with fixed tissues and stained sections from the case.

The microscopic changes of tissue removed during life have been described in published reports by Sattler,[4] Ohara,[5] Permar and Weil,[6] and McLaughlin and Jones,[7] and have been studied by Bruecken, McMeans and Sheehan.

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1. Verbrycke, J. R.: Tularaemia, with Report of a Fatal Case Simulating Cholangeitis, with Postmortem Report, J. A. M. A. **82**:1577-1581 (May 17) 1924.

2. Francis, Edward: Tularaemia, Handbuch der pathogenen Mikroorganismen, ed. 3, 1927, vol. 6.

3. Bruecken, A. J.: Unpublished history and autopsy report, St. Francis Hospital, Pittsburgh, May 23, 1926.

4. Sattler, Robert: Bacillus Tularense Conjunctivitis, Arch. Ophth. **44**: 265, 1915.

5. Ohara, Hachiro: Human Inoculation Experiment with a Disease of Wild Rabbits, with a Bacteriological Study, Kinsei Igaku, 1925, vol. 12, no. 5 (Japanese text); Experimental Inoculation of Disease of Wild Rabbits into the Human Body, Japan M. World **6**:300 (Nov. 15) 1926.

6. Permar, H. M., and Weil, G. C.: The Histopathology of the Subcutaneous Lesions in Tularaemia in Man, Am. J. Path. **2**:263, 1926.

7. McLaughlin, A. J., and Jones, W. M.: Tularaemia, Weekly Bull. St. Louis M. Soc. **20**:9 (May 20) 1926.

We wish to acknowledge our indebtedness to the physicians named in this article for their splendid spirit of cooperation in placing at our disposal the material which has formed the basis of this study.

REPORT OF CASES

CASE 1.—M. C., a negro woman, aged 35, was admitted Jan. 24, 1926, with shortness of breath, pain in the chest and a history of having had pneumonia four months previously. She was a patient of Dr. J. H. Wagner, at the St. Francis Hospital, Pittsburgh, Dr. A. J. Bruecken, pathologist. January 29, pneumonia involved the entire right chest and left lower lobe. February 13 an enlarged gland in the left axilla, the size of an egg, was first noted; this was thought to be secondary to some infection of the breast. March 3, a gland in the left axilla was removed; it was noted as being subpectoral; an abscess was encountered in dissecting the mass; several necrotic and abscessed glands were noted. March 13, the serum agglutinated *Bacterium tularense* in a maximum dilution of 1:320. Careful questioning elicited that the patient dressed rabbits about New Year's, 1926, but a cut or sore on the hands did not result. March 20, the patient was discharged, with the incision still unhealed. May 22, she was readmitted in coma, and she died May 23, at 12:33 a. m.

Autopsy was performed by Dr. A. J. Bruecken, ten hours after death. In the left axilla was a recent surgical incision, the skin edges of which were still ununited. The left lung contained enlarged peribronchial lymph nodes. At the apex was a calcareous area which was traced to a multilocular single cavity 1 cm. in diameter. At some distance there was a yellow tubercle. The right lung showed anthracosis of the lymph nodes. Minute fibrous tubercles were found. The mesentery did not show any evidence of enlarged nodes. Above the ileocecal valve some prominent nodules were seen. The lesser omentum showed several nonenlarged lymph nodes.

The liver at one point near the capsule showed a circumscribed nodule containing caseous material. At another point there was a similar nodule, chiefly fibrous. At the cystic duct there was an enlarged caseous lymph node, measuring 2.2 by 1.7 by 1 cm. The spleen was dark and soft. Through the capsule one could see a yellow node 0.5 cm. in diameter. Further section showed several other caseous nodules. The pulp was diffluent. The suprarenals showed opaque yellow and grayish translucent areas. The left axilla showed lymph nodes which were enlarged and contained yellowish foci. The urine was thick with albumin and showed granular casts and pus cells. Cultures of the heart blood showed *Streptococcus hemolyticus*. All efforts to demonstrate acid-fast organisms in smears or sections of autopsy material proved negative.

Guinea-Pig Inoculations.—Pig 1 was inoculated subcutaneously in the left groin with swollen axillary nodes of the patient taken at autopsy; the pig died during the tenth week; autopsy was performed a few hours after death. The left foot showed a rather large abscess which had been in progress since the fourth week; *Bacillus pestis caviae* was cultured from this abscess. The spleen showed abscesses somewhat resembling tubercles in the gross.

Pig 4 was inoculated with puriform material from a caseous lesser omental lymph node of the patient; at the end of eight weeks a swollen lymph node was

removed from the pig under anesthesia, but it did not reveal anything of interest; the pig died three days later showing abscesses of the spleen. It is thought that death was due to *B. pestis caviae.*

Pig 5, and a young rabbit, were inoculated with a bronchial lymph node of the patient. Pig 5 died in puerperal state one month after inoculation. The rabbit, while in excellent health, was killed Aug. 14, 1926, showing only coccidioidal nodules on the liver.

All efforts to demonstrate acid-fast organisms in smears or sections of experimental animals proved negative.

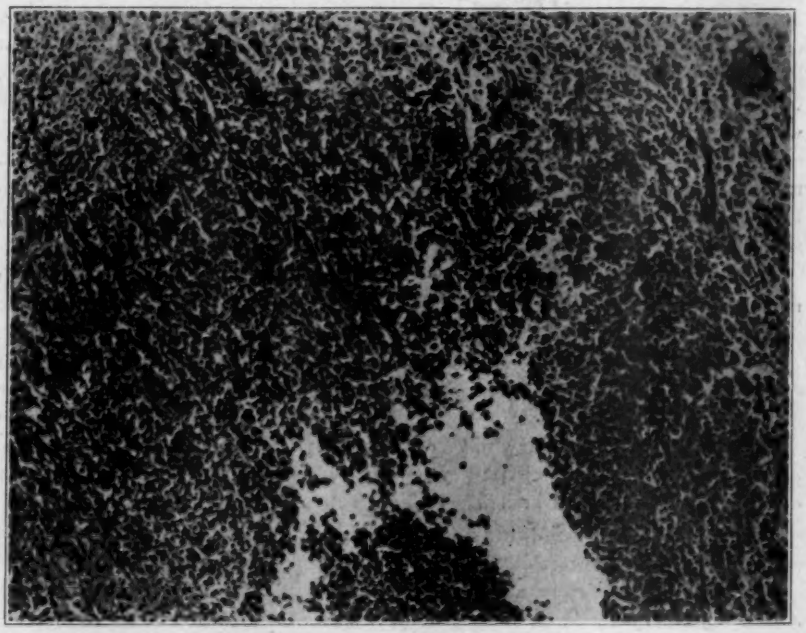

Fig. 1 (case 1).—Axillary n de at biopsy three months before death and about two months after infection; wall about necrotic center shows radiating fibroblasts between macrophage cells; marked leukocytic infiltration. × 100.

The material received was: a section of axillary lymph nodes removed March 3 and sections of microscopic material from the tissues at autopsy.

Biopsy.—Axillary lymph node: The lymph node showed a diffuse inflammatory reaction of moderate degree with some increase in connective tissue fibers. In it were several nodules which presented a thick wall made up of epithelioid cells interspersed with a few fibroblasts extending at right angles to the circumference of the nodule. This wall was densely infiltrated with leukocytes in which polymorphonuclears predominated slightly. In the center was a mass of lymphocytes, polymorphonuclears and epithelioid cells, many of the last containing polymorphonuclears and lymphocytes. This central mass did not contain any formed tissue and was essentially pus. In the wall, par-

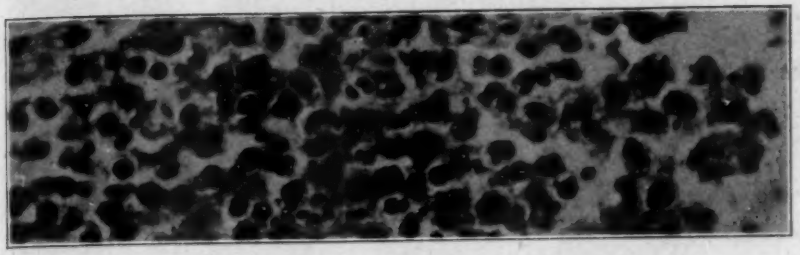

Fig. 2 (case 1).—High power magnification of central area of figure 1. × 400.

Fig. 3.—Reticulum in lesion of case 1 shown in figure 1. × 150.

Fig. 4 (case 1).—Lesion found at autopsy in bronchial node; central necrosis, fibrous wall and Langhans' cell; five months after infection. × 120.

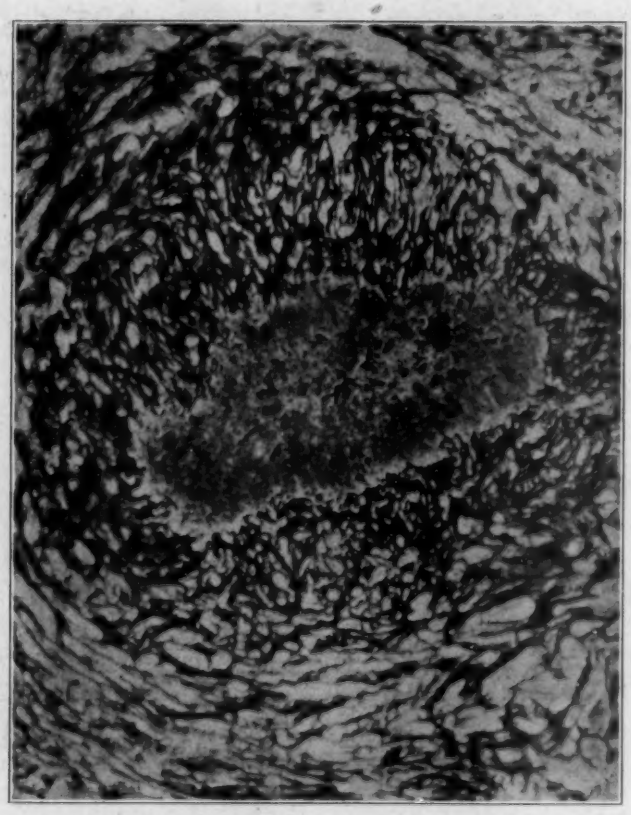

Fig. 5 (case 1).—Collagen stained in lesion similar to that of figure 4. × 175.

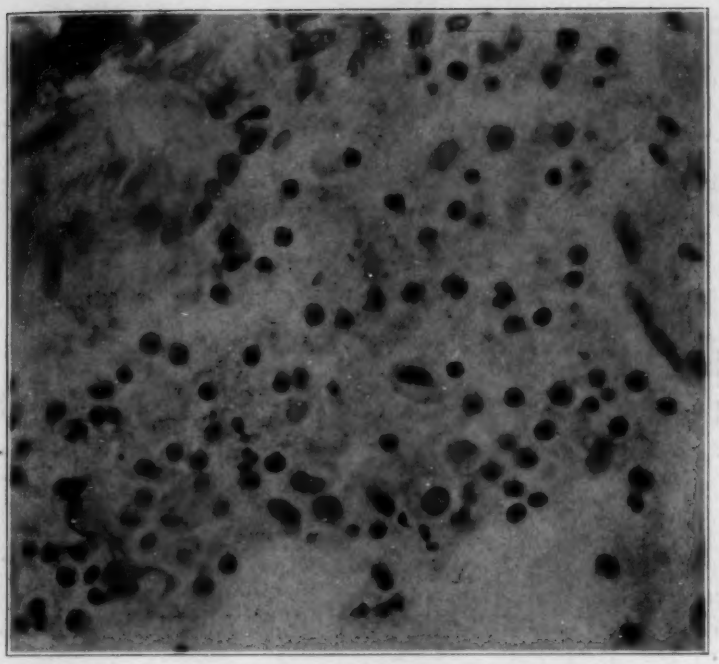

Fig. 6 (case 1).—Exudate in lymph space near lymph node. × 610.

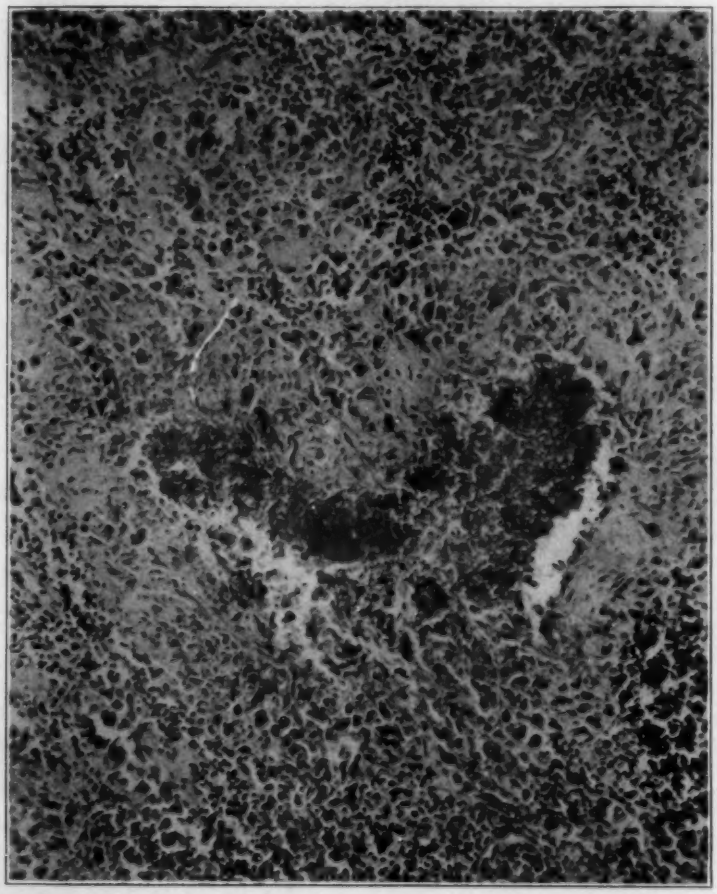

Fig. 7 (case 1).—Lesion in lesser omental node seen at autopsy. × 150.

ticularly in the outer border, cells of the Langhans' type were found (figs. 1 and 2). Reticulum was absent in this lesion, apparently not being formed, in spite of beginning organization as represented by fibroblasts (fig. 3).

Autopsy.—Axillary lymph node: There was considerable fibrosis throughout the tissue and a marked polymorphonuclear infiltration. The latter somewhat

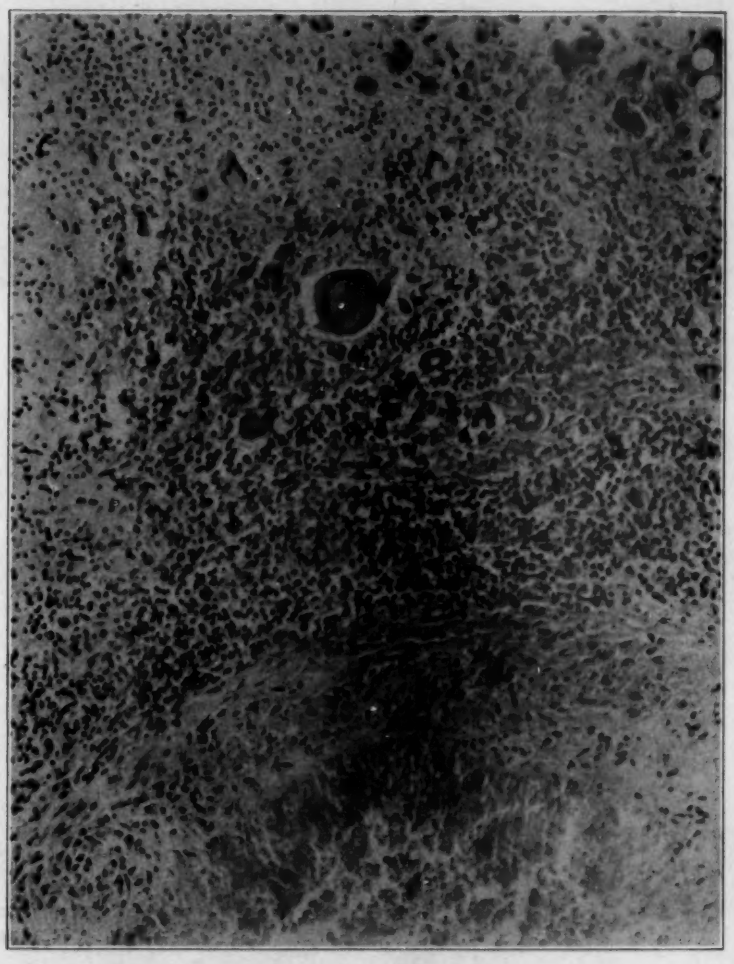

Fig. 8 (case 1).—Lesion in liver; liver cells at upper right corner; five months after infection. ×175.

obscured the picture in the lymph nodes which were involved in the secondary infection responsible for death. The tularemic foci in the node had necrotic centers, morphologic elements not being distinguishable therein, except leukocytes. The necrotic center was surrounded by a relatively narrow zone of radially placed fibroblasts infiltrated with a few epithelioid cells and many leukocytes.

Bronchial lymph node (fig. 4): The lesion in this node resembled those in the axilla almost exactly except for the lack of polymorphonuclear reaction. The description given previously for the axillary lymph node also describes this lesion; it will be noted that there are Langhans' cells in the outer portion (fig. 4). In this lesion reticulum is not produced in the wall of the necrotic area, but abundant collagen fibers have formed between the connective tissue cells. Figure 5 was taken from somewhat smaller lesions than that shown in fig. 4, the section being stained for both reticulum and collagen. Reticular fibers are seen in the surrounding tissue. The lymphatics draining these areas

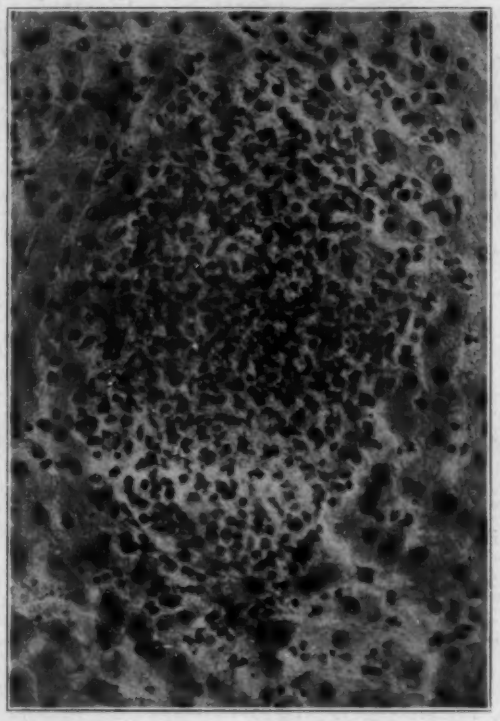

Fig. 9 (case 1).—Small nodule in liver. × 200.

frequently contained both polymorphonuclear and mononuclear leukocytes and macrophages (fig. 6).

Lesser omental lymph node: The node was hyperemic, the follicles were hyperplastic and one small nodule was seen. In this the center was necrotic and the surrounding zone was composed of fibroblasts and an unusually large number of macrophage cells, many containing lymphocytes. A few Langhans' cells were seen in the outer border (fig. 7).

Liver: Most of the lesions in the liver closely resembled those pictured in the bronchial lymph node. A section of a margin of one of these is shown in figure 8. Surrounding the organized wall there was a diffuse increase in fibrous tissue densely infiltrated with lymphocytes and containing numerous cells of Langhans' type. Fibers of this tissue penetrated between the cords of liver

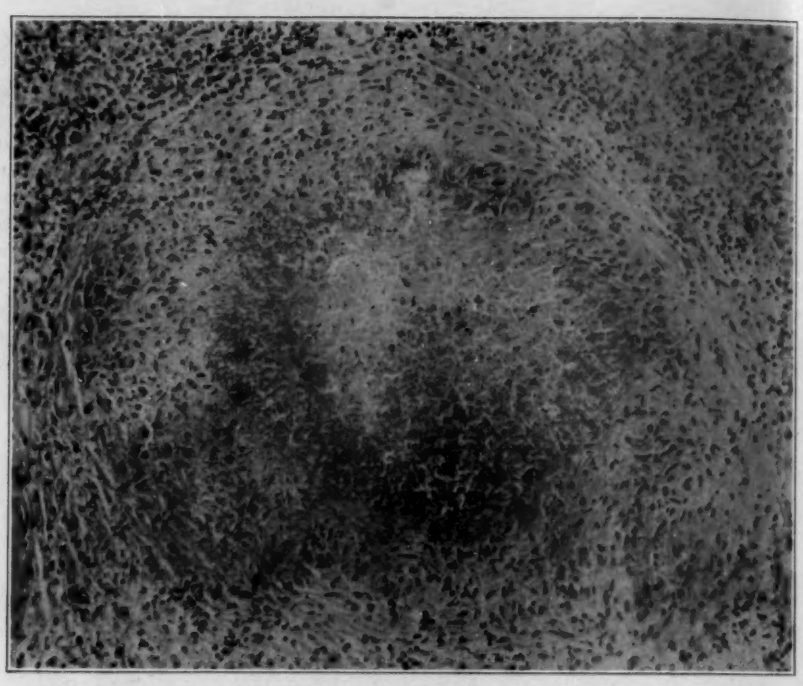

Fig. 10 (case 1).—Nodule in spleen; comparison should be made with figures 4, 7 and 8. × 120.

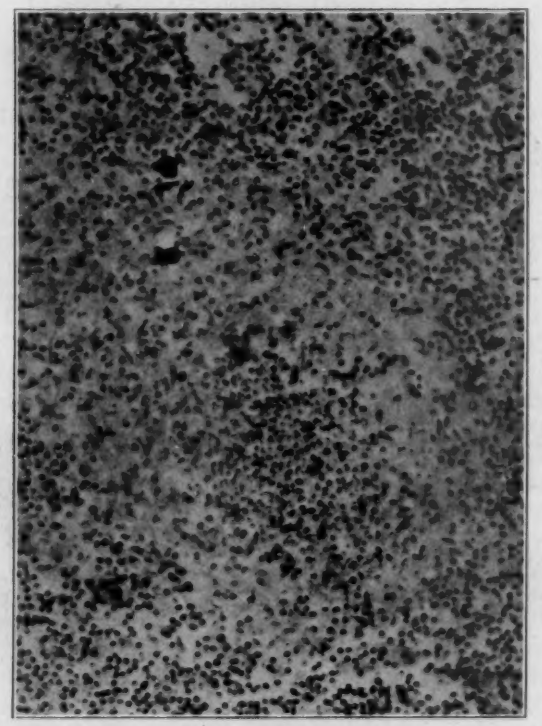

Fig. 11 (case 1).—Small nodule in axillary lymph node removed at biopsy two months after infection. × 135.

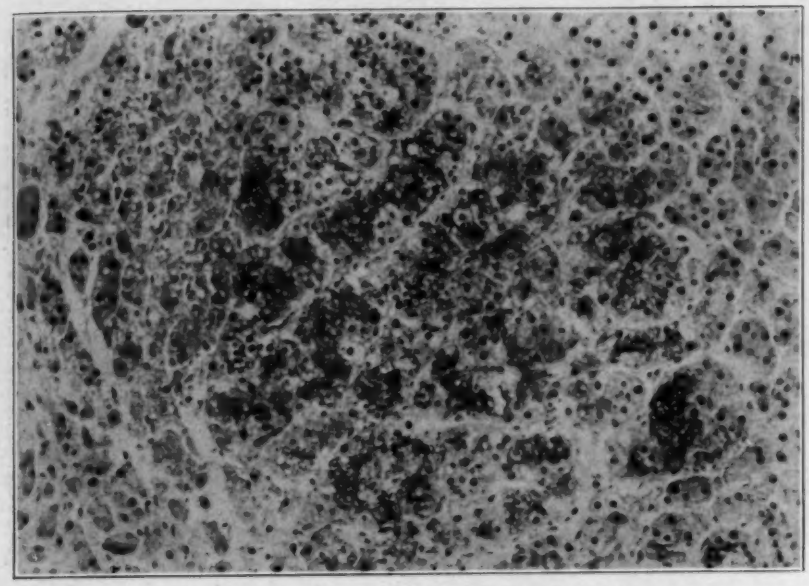

Fig. 12 (case 1).—Lesion in suprarenal. × 150.

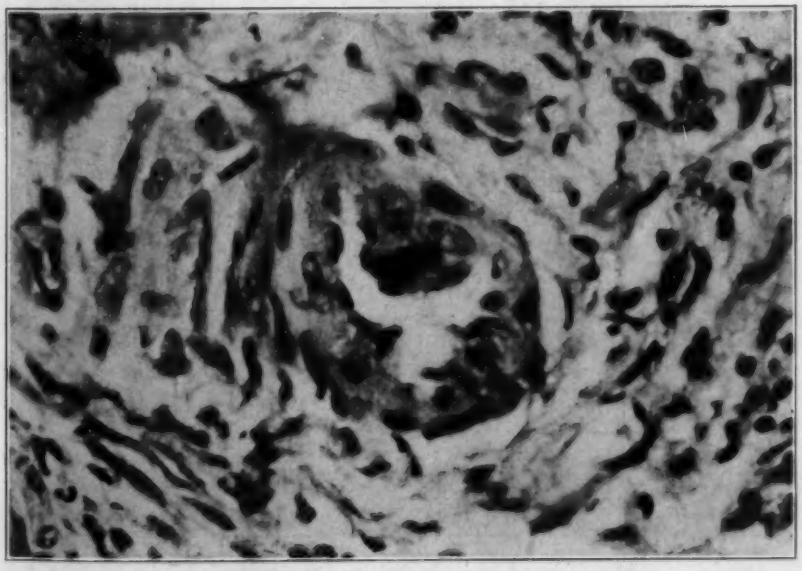

Fig. 13 (case 1).—Blood vessel; swelling and proliferation of endothelium. × 640.

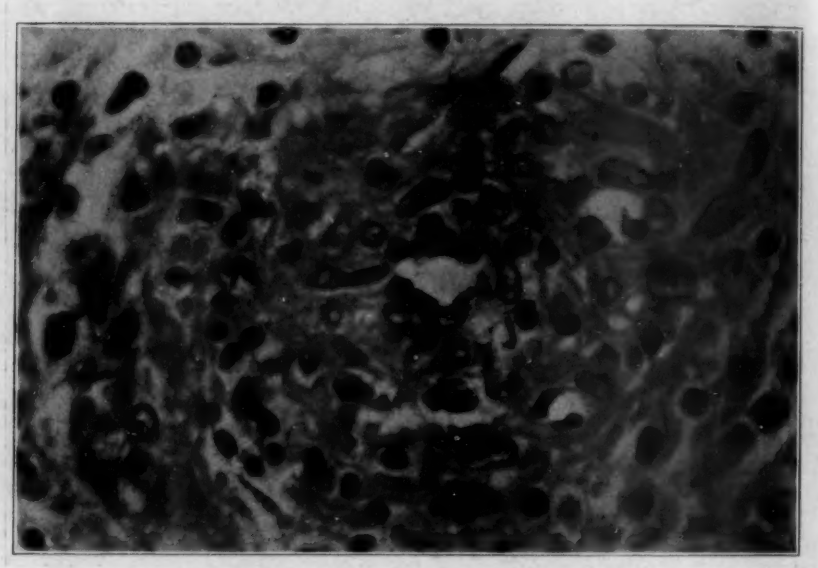

Fig. 14 (case 1).—Obliterative endarteritis, later stage than shown in figure 13. ×640.

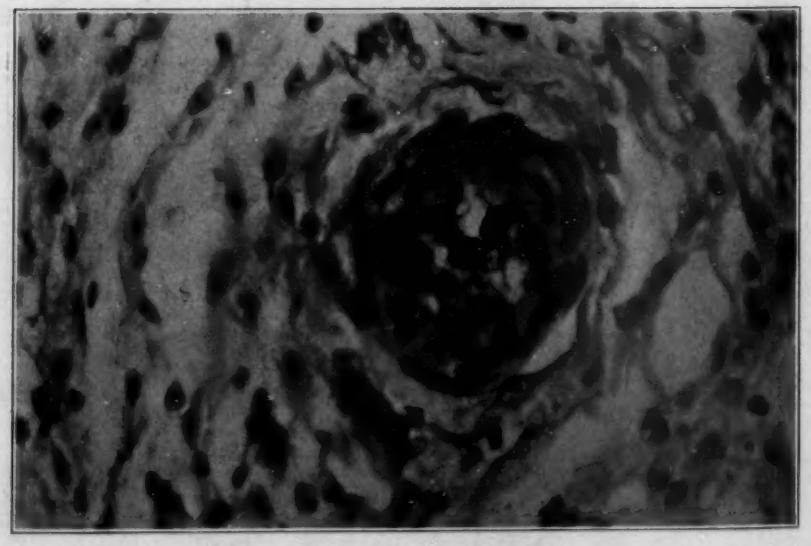

Fig. 15 (case 1).—Obliterative endarteritis; vessel practically closed. ×870.

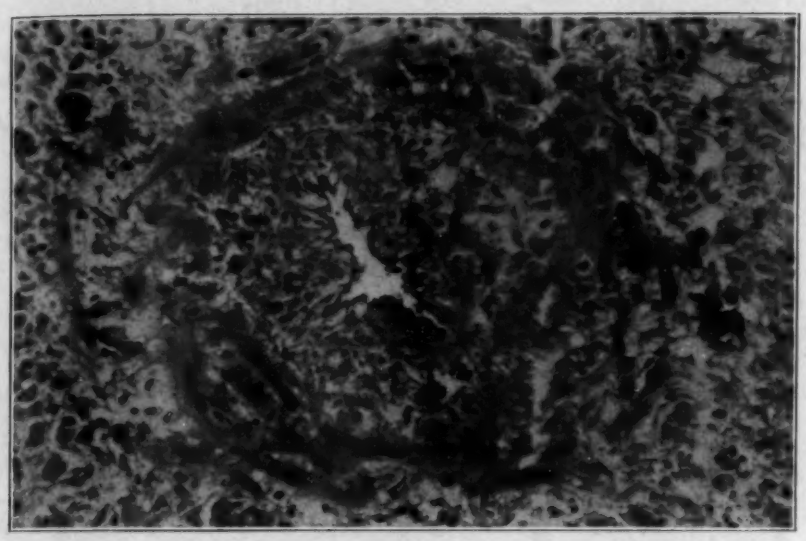

Fig. 16 (case 1).—Obliterative endarteritis; hematoxylin and eosin stain. × 175.

Fig. 17 (case 1).—Obliterative endarteritis; reticulum stain. × 175.

cells blending with the general structure of the liver. Epithelioid cells, some of them containing lymphocytes, were rather more abundant in the liver than in the other tissues. There were also numerous lesions of small or miliary size in the intermediate zones of the lobules. These were composed of masses of epithelioid cells densely infiltrated with leukocytes, the majority of which were mononuclears (fig. 9).

Spleen: The lesions in this organ were similar to those in the liver, having abundant fibroblastic increase surrounding them. One is illustrated in figure 10. Smaller lesions also were present in the spleen, and were identical in appearance with the smaller lesions seen in the axillary nodes. They presumably represented an early stage in the formation of a nodule (fig. 11). They consisted of a mass of epithelioid cells containing a few fibroblasts, while the center contained many leukocytes and was undergoing necrosis.

Suprarenal (fig. 12): Scattered throughout the cortex were necrotic or partially necrotic foci placed somewhat nearer the medulla than the periphery. These showed necrosis of glandular cells, considerable edema and leukocytic infiltration. Evidence of macrophage reaction or fibroblastic increase was not seen.

Kidney: There were secondary degenerative changes, but not any lesions which were attributable directly to tularemia.

Blood vessel lesions: The blood vessels near the tularemic lesions as seen in the autopsy tissues showed a change described first by Permar and Weil. This change consisted in a swelling of the endothelial cells and an edema of the wall of the vessel. The endothelial cells proliferated narrowing the lumen even to complete obliteration (figs. 13, 14 and 15). This proliferation was accompanied by a marked increase in reticulum as shown in figures 16 and 17, which are sections of the same vessel, hematoxylin and eosin stains being used in figure 16 and reticulum stain in figure 17.

Case 2.—In C. S., a white woman, aged 67, a housewife, the source of infection was two rabbits bought in the Washington market and dressed by her for the family table on Dec. 8, 1923. The case was reported by Dr. J. R. Verbrycke, Garfield Memorial Hospital, Washington, D. C., Dr. Maurice Sellinger, pathologist. The onset of illness occurred on December 13. Blood serum collected on the sixteenth day of illness agglutinated *Bacterium tularense* in a maximum dilution of 1:80. Cultures of *Bacterium tularense* were obtained at the Hygienic Laboratory from guinea-pigs, rabbits and white mice which died acutely manifesting the typical lesions of tularemia after inoculation with spleen tissue obtained at the necropsy December 31.

The necropsy was performed several hours after death, eighteen days after the onset of illness and eight days after an exploratory abdominal incision. The lungs showed in the lower left lobe, and in the upper and lower right lobes, small discrete nodules about the size of small shot, distributed over the surface and in the parenchyma; one, however, was about the size of a walnut. Enlarged and caseous peribronchial lymph glands showing a moderate degree of anthracosis were noted in the right upper lobe. The liver did not show any gross lesions. The spleen was unusually soft, and scattered over its surface and throughout the pulp were many small circumscribed, firm, yellowish white nodules, about the size of millet seed. Enlarged lymph glands were not noted in other parts of the body.

Tuberculosis of the spleen was excluded by the following guinea-pig tests. A portion of the patient's spleen was placed at 4 C. in a stoppered bottle for one month, it having been established that tularemia infection will not survive

one month in a rabbit spleen kept under similar conditions. At the end of the month a portion of the spleen was injected subcutaneously into guinea-pigs, which remained well. As a control, the spleen of a guinea-pig dead of tuberculosis was placed under similar conditions at 4 C., and a small portion was injected subcutaneously each week into a fresh guinea-pig for eight weeks.

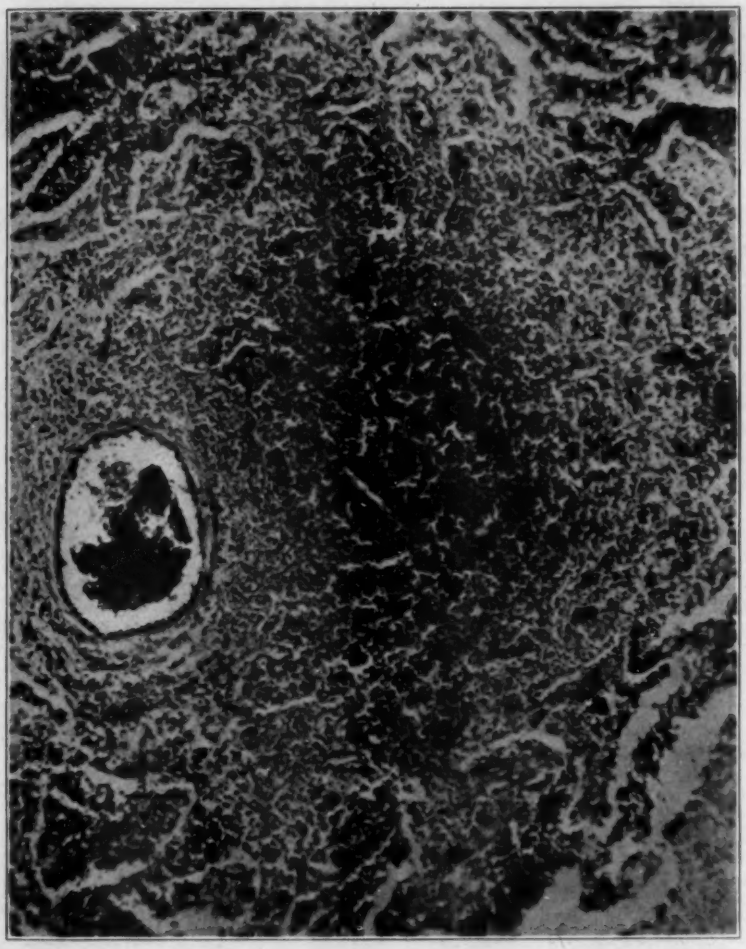

Fig. 18 (case 2).—Low power section from small lesion in lung eighteen days after onset.

The entire series of eight pigs died with typical lesions of tuberculosis of the spleen and caseation of inguinal glands.

Tubercle bacilli could not be demonstrated in specially stained sections of two pieces of the patient's spleen tissue, two lymph nodes of the right lung, and one lymph node of the left lung.

The pathologic condition of this case was difficult to interpret as there was an acute purulent bronchopneumonia in the lungs, and there were some active

tubercles in the bronchial lymph nodes in addition to the lesions of tularemia; the latter, however, were sufficiently characteristic, in the light of cases examined subsequently, to render possible the definition of the lesions due to *Bacterium tularense*.

Lung: Areas varying in size from 1 to 4 or 5 mm. were found in the tissue adjacent to bronchioles and their surrounding vessels, apparently arising in the lymphatic structures and extended varying distances into the parenchyma of the lung (fig. 18). They presented a fibroblastic increase of varying depth on the periphery in which the blood vessels of small caliber showed a proliferation of the endothelial lining, at times obliterating the structure. The central portions of such areas were necrotic, and the whole mass was infiltrated with leukocytes, at least 50 per cent of which were lymphocytes. At the margin,

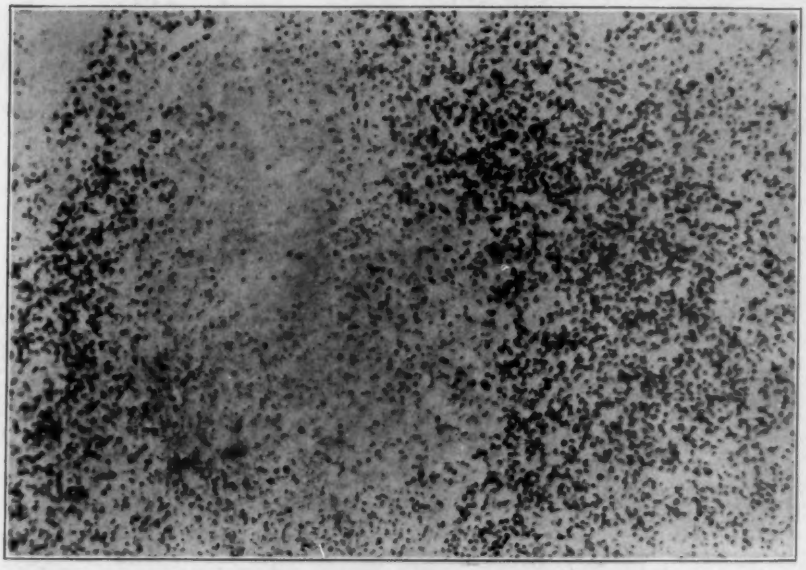

Fig. 19 (case 2).—Spleen; nodule eighteen days after onset.

which was irregular, masses of fibroblasts infiltrated with lymphocytes extended into the alveoli, and the alveolar walls were thickened by connective tissue increase. Toward the necrotic area macrophage cells were seen in moderate numbers. In two of the nodes at the hilus of the lung there were areas similar in gross appearance to those seen in the parenchyma. These consisted of a margin of fibroblasts, with numerous macrophage cells next in order, and in the center necrotic material containing tissue detritus.

Spleen: The organ was generally congested and in gross appearance showed numerous necrotic pale areas from one to several millimeters in diameter. Microscopically these consisted of a relatively narrow zone of fibroblasts, a relatively wide zone of large mononuclear cells and a small area of complete necrosis. The smallest areas contained only macrophage cells and leukocytes replacing the normal structure. These lesions appeared to arise in the outer part of or adjacent to the lymph follicles (fig. 19).

Liver: Necrotic areas of various sizes were seen in this organ which in a general way resembled those in the lung and the spleen. The larger ones showed a considerable amount of central necrosis and the macrophage reaction was much more intense. Collections of these cells infiltrated with lymphocytes and polymorphonuclear leukocytes formed minute miliary lesions in the intermediate zones of the hepatic lobule.

CASE 3.—In R. S., a white man, aged 52, a farmer of Delta, Utah, the source of infection was a fly bite on the right side of the neck posteriorly. This case was reported by Francis. Cultures of *Bacterium tularense* were obtained from guinea-pigs inoculated with (1) blood collected on the fourth day of illness, (2) pus collected from the suppurating right posterior auricular gland on the fourteenth day and (3) spleen tissue taken at necropsy Aug. 18, 1919, eighteen hours after death and twenty-six days after the onset of illness. A secondary pneumonia of the right upper lobe accompanied by much pain and by rusty sputum existed during the last few days of life. Necropsy went no further than to expose the spleen and liver. The spleen was studded over the entire surface and throughout the pulp with white nodules from 1 to 3 mm. in diameter. The nodules had a capsular wall from which the caseous contents were readily shelled out. The liver apparently was normal on inspection of its surface. Fixation of spleen tissue was poorly performed by placing half of the spleen en masse in pure methyl alcohol.

The material examined was a small section of spleen. Grossly there were numerous miliary and submiliary necrotic foci scattered throughout, more numerous near the capsule. Microscopic examination showed them to be small necrotic areas surrounded by a delicate zone of fibroblasts interspersed with relatively numerous macrophage cells.

CASE 4 (volunteer inoculation).—In R. O., a housewife, in Fukushima, Japan, the source of infection was the heart of a rabbit which was found dead in a district in which numerous human cases had developed recently. This case was reported by Ohara and quoted by Francis and Moore.[8] Blood and tissue fluids of the rabbit heart were rubbed lightly into the back of the patient's left hand, and about twenty minutes later the adherent material was washed off with soap. The onset of symptoms occurred two days later (Jan. 22, 1925). Sixteen days following the onset, two axillary glands the size of a pigeon's egg, and several smaller ones, were removed from the left axilla; the two larger glands had undergone suppuration. The patient did not present any clinical evidence of tuberculosis either before or after inoculation. Blood serum collected eight months after the onset agglutinated *Bacterium tularense* completely in dilutions of 1:10 and 20, and partially in dilution of 1:40.

The tissues examined were sections of axillary lymph node. The lesions of the node were characterized by a broken up central mass composed of large macrophage cells, lymphocytes and polymorphonuclear leukocytes. This was surrounded by an area composed largely of macrophage cells with an occasional fibroblast combined in organized tissue and containing occasional Langhans' cells. The outer part of this area merged gradually with the surrounding structure of the lymph node, the macrophage cells becoming less numerous as distance from the main lesion increased. Little evidence of fibroblastic resistance was displayed in this case. Cells of Langhans' type were seen in and outside the wall surrounding the necrotic area (fig. 20).

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8. Francis, Edward, and Moore, Dunlop: Identity of Ohara's Disease and Tularaemia, J. A. M. A. **86**:1329 (May 1) 1926.

Case 5.—In A. R. C., a man, aged 38, a waiter in St. Louis, Mo., the source of infection was probably rabbits which he shot the last week in September and late in November, 1925, or which he bought, dressed and washed, on two occasions. This case was reported by McLaughlin and Jones. Symptoms of an acute onset were lacking, but early in December the patient noticed a sore on the left thumb and on December 10 a swelling in the left axilla. At the time of the first

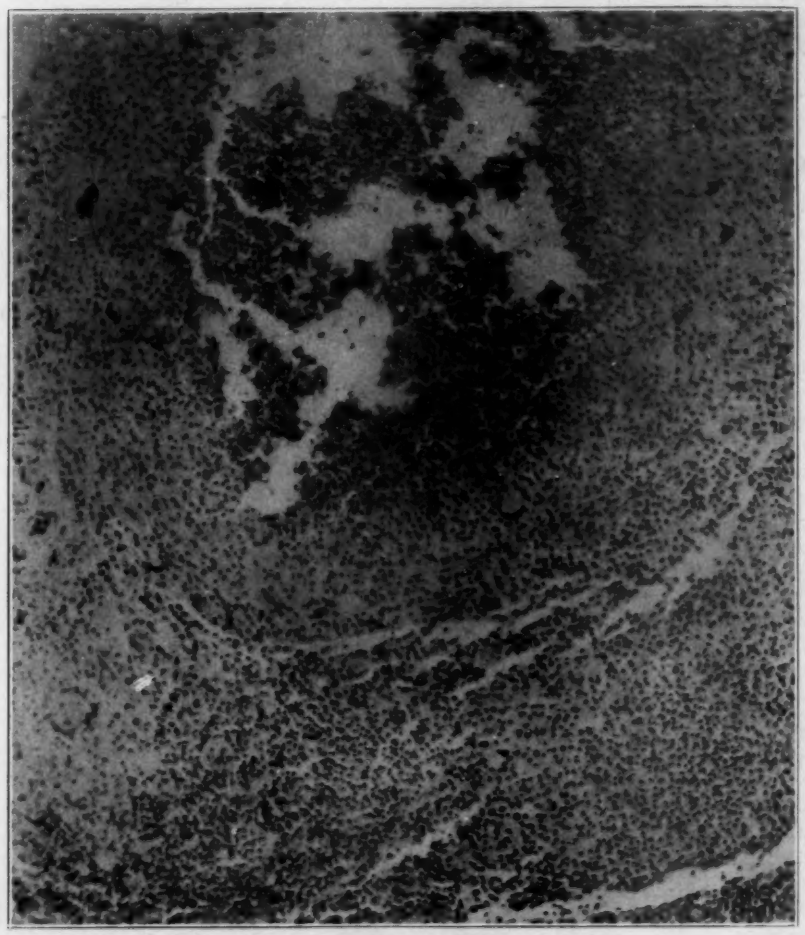

Fig. 20 (case 4).—Axillary lymph node removed sixteen days after onset; central area of leukocytes; wall of histiocytes and fibroblasts with occasional Langhans' cells, infiltrated with leukocytes. × 120.

medical examination on December 29 a small infected sore of the left thumb was incised, a chain of subcutaneous nodules the size of peas was noted between the wrist and elbow, the epitrochlear gland was enlarged and in the left axilla there was a glandular enlargement the size of an egg. Guinea-pigs inoculated with pus from the finger remained well for six weeks and at autopsy gave

negative observations. Suppuration occurred in the subcutaneous nodules and in the axillary gland. Jan. 4, 1926, a small nodule was excised from the left wrist over the anterior surface of the end of the radius. March 25, the axilla was dissected, and a conglomerate mass adherent to the axillary vessels and brachial plexus was removed with difficulty. A portion of this mass was sent to the Hygienic Laboratory, Washington, D. C., on which Surgeon G. C. Lake,

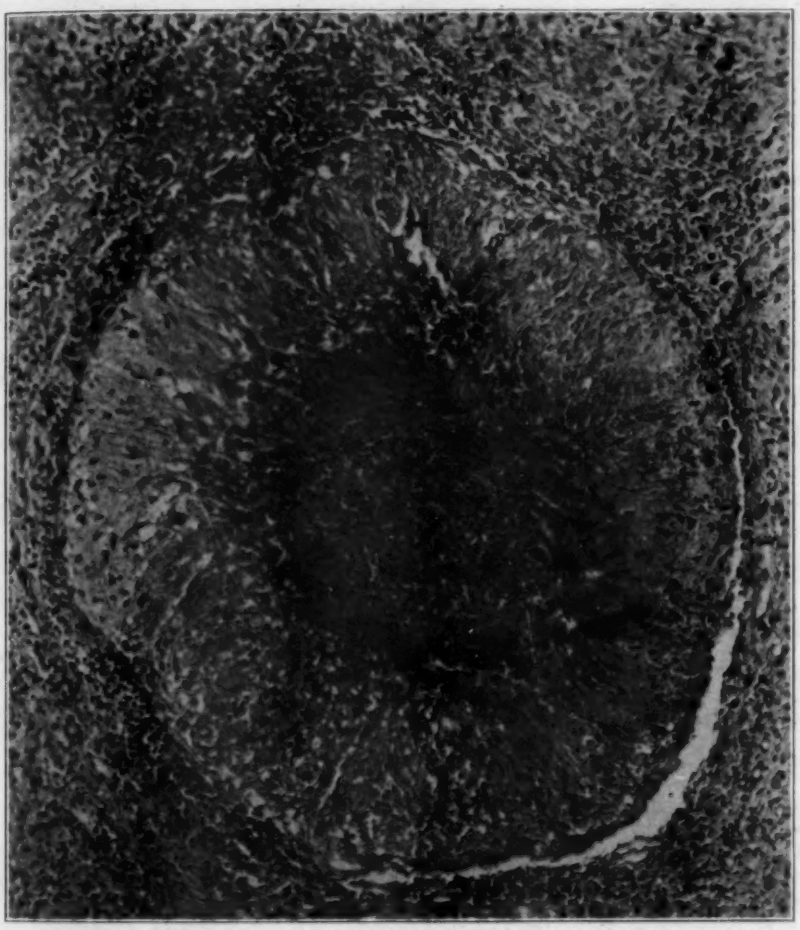

Fig. 21 (case 5).—Axillary lymph node removed four months after onset; fibrous wall surrounding a necrotic amorphous center. × 120.

U. S. Public Health Service reported extensive caseation necrosis, the absence of tubercle bacilli and the presence of Langhans' giant cells, suggested the diagnosis of tularemia and requested a sample of the patient's blood serum. Serum collected April 15 was found to agglutinate *Bacterium tularense* in dilutions of 1:10, 20, 40, 80, 160 and 320, thus confirming the histologic diagnosis of tularemia.

The specimens consisted of histologic material from a skin nodule and an axillary lymph node. The lesion in the skin appeared to arise in the dermal

lymphatics, the characteristic changes were partially surrounded by a zone of lymphocytes although a lymph node structure was not present. The essential lesion was characterized by a necrotic center surrounded by a radiating zone of fibroblasts and then by a diffuse fibroblastic increase rather densely infiltrated with lymphocytes. In the fibroblastic area of the outer zone were seen occasional Langhans' cells. This surrounding fibrosis blended with the dermal connective tissue, and many of the small blood vessels contained therein showed proliferative changes in the endothelial lining. The fibrosis surrounding the lesion was quite dense and in places hyalin in appearance. The axis of the cells appeared to be at right angles to the necrotic center. In the axillary lymph node the same type of lesion was found but the surrounding diffuse fibrosis was not as evident as it blended, at the margin of the radiating fibrosis, immediately with the surrounding structure of the lymph node. The lesions in the lymph nodes were distinctly focal in nature, the larger ones being surrounded by others of much smaller dimensions (fig. 21).

Case 6.—In F. K., a man, aged 47, a butcher in St. Louis, Mo., infection took place in a scratch made on the ring finger of the right hand by a broken rabbit bone while he was dressing rabbits. This case was reported by Dr. George J. Epp of St. Louis in the discussion of the case reported by McLaughlin and Jones. Nov. 30, 1925, four days after the scratch, a papule developed at the site of the scratch; this finally broke down forming a necrotic ulcer. A few days following the appearance of the papule from twenty-five to thirty small nodules were noticed extending from the infected finger to the axilla. They varied in size from that of a pea to 1.5 cm. in diameter and were located on the dorsal and flexor surfaces of the right forearm and on the lateral and posterior surfaces of the right arm. These nodules were firm, freely moveable and painful on palpation. In time twenty-seven of them were either excised or incised; all suppurated. Jan. 23, 1926, an abscess of the right axilla was incised and about 250 cc. of pus escaped. Blood serum collected on May 23, agglutinated *Bacterium tularense* in dilutions of 1:10, 20, 40, 80 and 160, thus confirming the diagnosis of tularemia. On May 23, a subcutaneous nodule was removed from the posterolateral aspect of the lower third of the right arm for microscopic study.

The material examined was a subcutaneous nodule. This nodule showed the general reaction seen in other cases; namely, a radial area of fibroblasts and fibers about the central necrotic area surrounded by more or less diffuse fibrosis which blended with the surrounding tissue. Vascular structures showed proliferative lesions in the intima and there were more or less numerous Langhans' cells in the outer area usually outside of the radiating fibers. The fibrous wall in the lesion in this case was more cellular than that in any other case examined. It had greater width although nuclei were relatively abundant. Macrophages were relatively scanty (fig. 22).

Case 7.—Mrs. M. H., aged 48, admitted at the Mercy Hospital, Pittsburgh, had scratched her right thumb on a splintered rabbit bone on Nov. 19, 1925, while dressing wild rabbits. The onset of the illness occurred on November 22. The site of infection suppurated, and inflammatory nodules soon developed on the flexor surface of the forearm, some of which required drainage. Feb. 1, 1926, a subcutaneous nodule on the forearm and an axillary abscess were drained. February 24, two subcutaneous nodules which were located on the upper arm over the biceps region, and which were of about two weeks' duration, were excised for microscopic study; sections stained by the Gram-Weigert and by

the Ziehl-Neelson method did not reveal bacteria of any type. Blood serum collected Feb. 10, Feb. 19 and March 20, 1926, agglutinated *Bacterium tularense* in a maximum dilution of 1:160.

This case was reported by Drs. Permar and Weil and the subcutaneous lesions were thoroughly described. Our observations in their sections of tissue removed February 24 and in others from similar cases are in agreement with

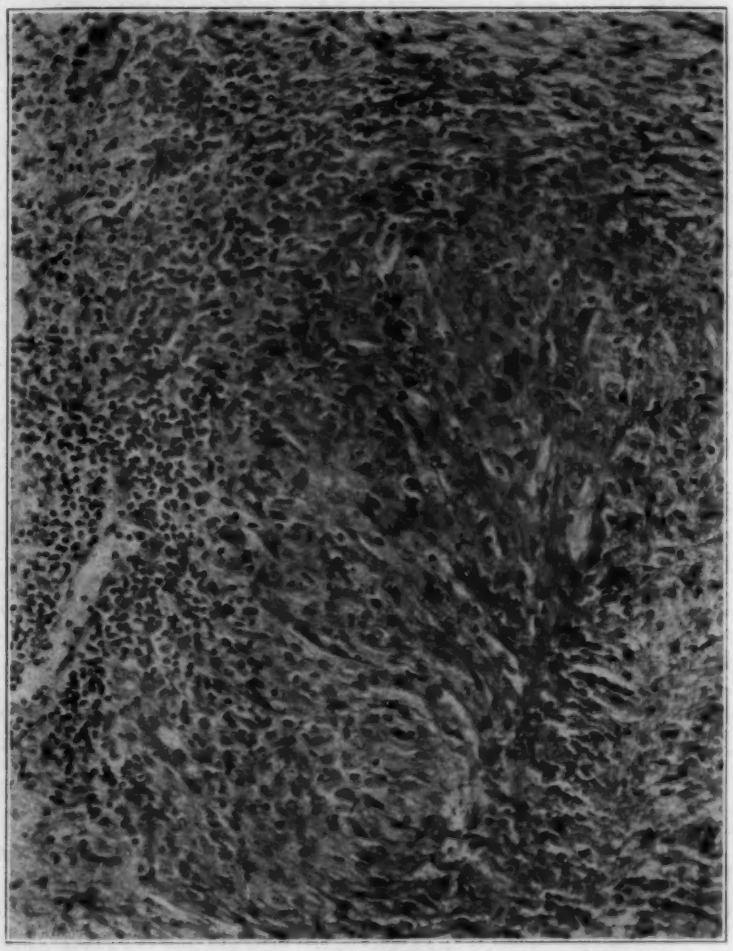

Fig. 22 (case 6).—Subcutaneous nodule removed six months after date of infection; dense fibroblastic wall which is cellular; Langhans' cell in surrounding tissue. × 140.

theirs. To quote from their report: "The sections show circumscribed inflammatory nodules lying below the dermis . . . the process apparently originated in lymphatics. A typical inflammatory nodule shows a necrotic center . . . . surrounding this is a narrow zone of . . . partly degenerated endothelial leukocytes . . . just beyond this is . . . a clearly marked zone of newly formed

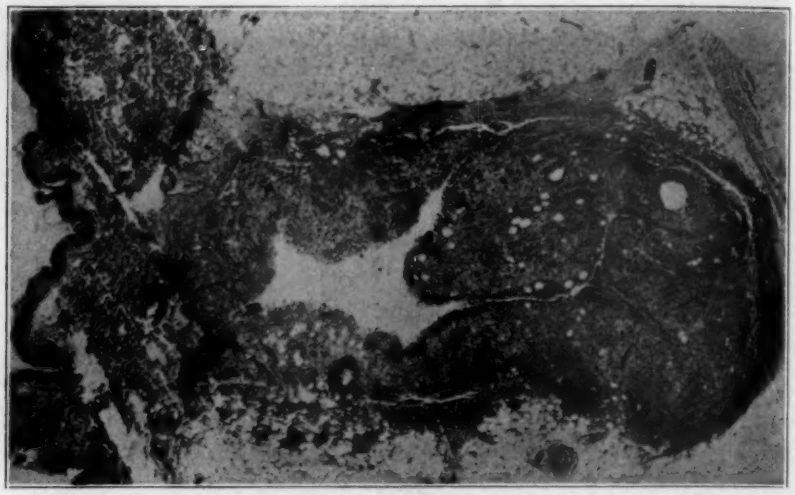

Fig. 23 (case 7).—Subcutaneous nodule; central necrotic mass absent through technical procedure. × 10.

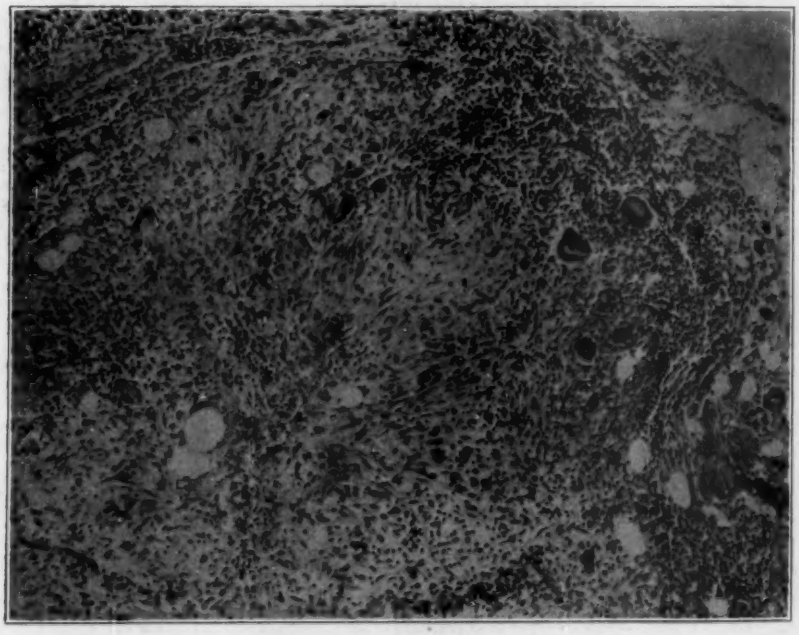

Fig. 24 (case 7).—Area from section shown in figure 23. × 120.

tissue . . . the capillaries in this zone . . . are few . . . with narrow lumina as a result of hyperplasia of the endothelium . . . a striking and unusual finding is encountered in the presence of many large giant cells much like the Langhans' type." (Figs. 23 and 24.)

Case 8.—Mrs. E. R., aged 40, a patient of Dr. C. A. Hamann, was admitted to the St. Vincent Charity Hospital, Cleveland, Dr. William J. Sheehan, pathologist. While dressing a rabbit, in November, 1925, she cut the middle finger of her left hand. The onset of illness occurred several days later, with headache, fever and prostration. She was in bed for about six weeks and when she got up there was a swelling on the medial side of her left arm in the region of the middle third of the humerus.

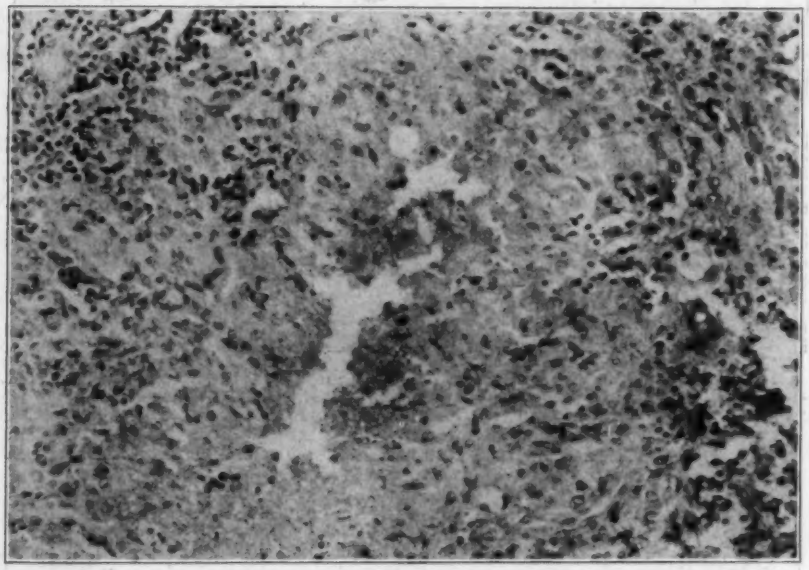

Fig. 25 (case 8).—Fibrous focal lesion in axillary node removed nine months after onset. × 200.

When first seen in August, 1926, the patient presented a fusiform swelling on the medial surface of the left arm, at the middle third of the humerus. One of the left axillary glands and several infraclavicular glands of the opposite side were enlarged. The gland on the humerus was excised and was suppurating; two guinea-pigs and a rabbit were inoculated with this material. The animals remained well over a period of twelve weeks.

The material for sections consisted of pieces from the humeral gland and from the axilla, but the two tissues were not kept separate. Unstained slides were received Aug. 21, 1926.

Serum collected August 17, agglutinated *Bacterium tularense* in a dilution of 1:160, but not in a higher dilution.

The material received was sections from a nodule on the arm in the subcutaneous tissue and axillary node.

The subcutaneous tissue showed a diffuse fibrosis with endothelial proliferation in the vessels. In this tissue were foci with necrotic centers surrounded by a wall of radially placed fibroblasts rather closely opposed, and with relatively little collagen. The necrotic centers contained a considerable number of leukocytes.

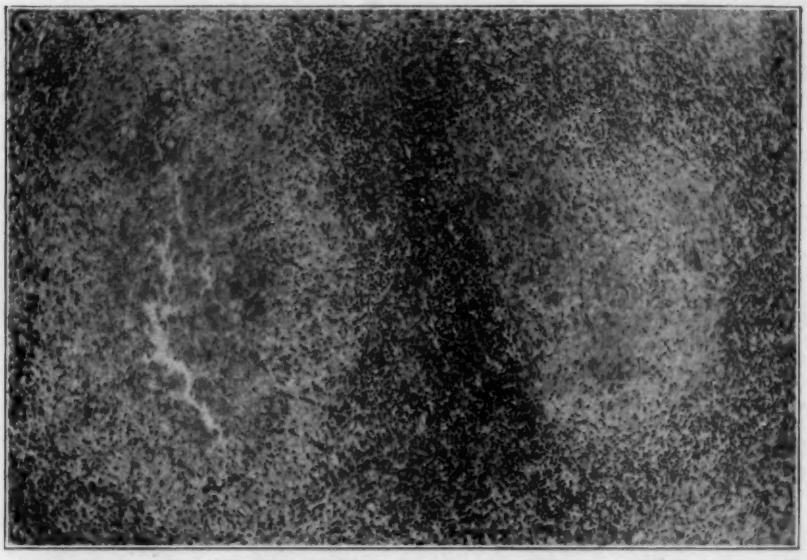

Fig. 26 (case 9).—Axillary node lesions removed forty-two days after onset. × 125.

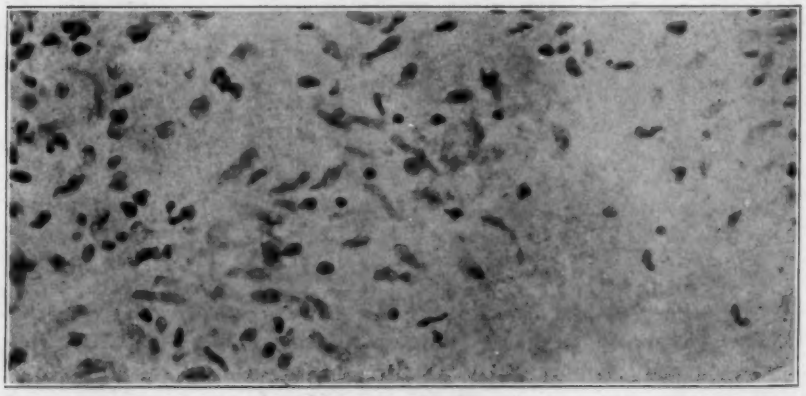

Fig. 27 (case 9).—High power reproduction of margin of nodule of figure 26; fibroblasts extending into necrotic center.

Axillary node: The entire structure showed considerable fibroblastic increase so that the outlines of the node could not be defined. There were numerous foci throughout with necrotic centers, and radially placed fibroblasts formed the periphery. Langhans' cells were present but not particularly numerous (fig. 25).

CASE 9.—M. S., a man, aged 48, a produce dealer, a patient of Dr. H. F. Zinsser, admitted to St. Margaret Hospital, Pittsburgh, Dr. J. W. McMeans, pathologist, had recently dressed hundreds of rabbits but did not recall any injury. He first noticed a papule on the dorsum of the right hand (anatomic snuffbox) about Jan. 3, 1926. The definite onset of illness dated from January 11 and was characterized by chills, fever, pains and prostration. The papule became an ulcer and the right axillary glands became the size of a walnut and suppurated. About February 4, a small swelling developed along the extensor surface of the right arm which was opened and drained. Serum collected February 11 agglutinated *Bacterium tularense* in a dilution of 1:640, but not in higher dilution. On February 22, the axillary glands were removed, stained sections of which were sent to us by Dr. J. W. McMeans. The material consisted of axillary nodes.

Numerous tularemic lesions were scattered throughout the lymph tissue, the smallest of miliary size consisted of groups of fibroblasts containing a few macrophages, an occasional Langhans' cell and a few polymorphonuclears and lymphocytes; the larger areas had an outer border of fibroblasts from which radiating connective tissue cells extended toward the center which was necrotic. There were a few macrophages bordering on the necrotic area, and the necrotic contents apparently were composed of these cells and leukocytes. There was considerable diffuse fibrosis throughout the node and the fibroblasts appeared to be organizing the necrotic center (figs. 26 and 27).

CASE 10.—F. S., a man, aged 40, white, a market man, scratched his finger while dressing a rabbit and a few days later, on Nov. 20, 1926, again scratched his finger while dressing another rabbit. November 23 the onset of illness occurred, followed by enlargement of the right epitrochlear and axillary lymph nodes, and an ulcer on the right index finger. He was admitted as a patient of Dr. J. H. Wagner, to St. Francis Hospital, Pittsburgh, Dr. A. J. Bruecken, pathologist. December 5, Dr. Wagner excised the axillary mass. Dr. Bruecken fixed part of this tissue in Zenker's solution and inoculated another part into two guinea-pigs. The pigs died with typical lesions of tularemia, and *Bacterium tularense* was cultured from the spleen. Blood serum collected November 30, failed to agglutinate *Bacterium tularense;* this is in accord with serums tested on the seventh day of illness in tularemia.

The report of case 10 was received after we had written up the preceding cases, but as the lesions are apparently the earliest yet studied in point of time after the onset of illness (twelve days) and, further, as they more closely resemble the lesions in the spleen of the guinea-pig (fig. 32) it is thought advisable to include a description of them in this paper. Such early lesions are much less characteristic of the pathology of tularemia in man than those found later, after some opportunity has been afforded for immunity to develop. Agglutinins were not present five days before the excision of the axillary mass.

The material received consisted of sections of the axillary mass.

Histologic examination showed that the sections were from the lymph node and surrounding tissue. The surrounding tissue was markedly edematous and infiltrated with leukocytes and endothelial cells. Polymorphonuclears appeared to predominate. The blood vessels showed a marked thickening of the walls.

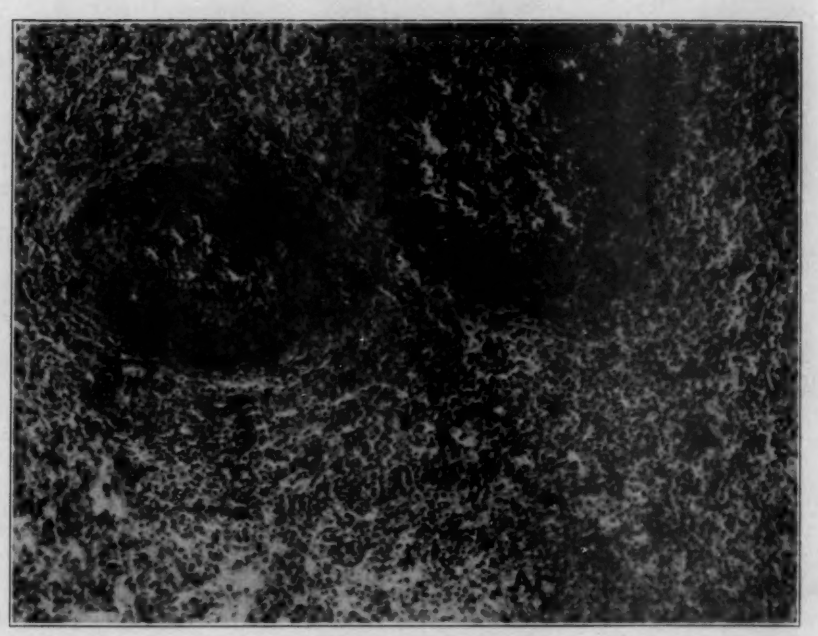

Fig. 28 (case 10).—Axillary lymph node lesion twelve days after onset of illness. × 120. Comparison should be made with lesion in spleen of guinea-pig (fig. 32). *A* indicates giant cell.

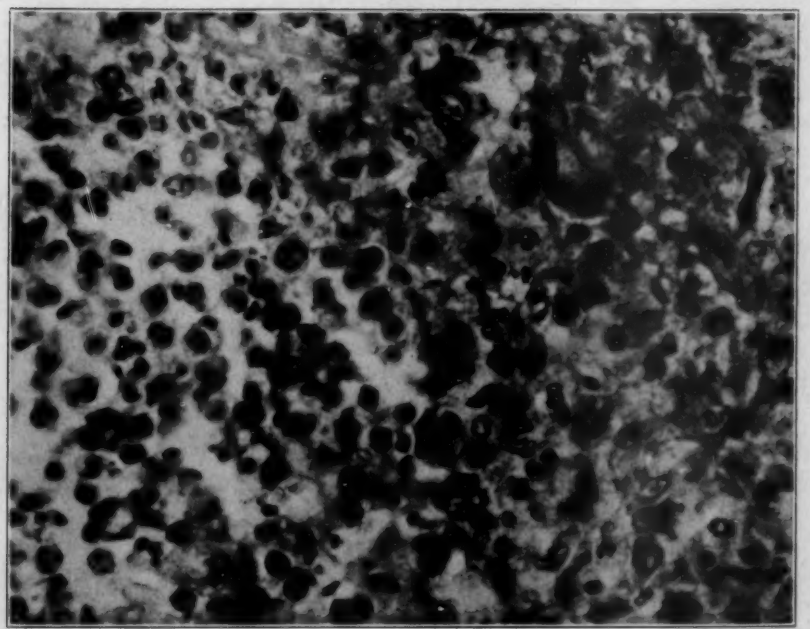

Fig. 29 (case 10). Section of one of the nodules in figure 28. × 350. *A* indicates giant cell.

particularly the subendothelial layer. The lymph node showed an obliteration of the markings by inflammatory edema and infiltration of polymorphonuclear leukocytes, together with a marked proliferation of the reticulum of the node which was most marked toward the periphery. There were numerous foci of varying size composed of a center filled with polymorphonuclear and mononuclear leukocytes and many macrophages (fig. 28), many of the latter having encysted mononuclear leukocytes and occasionally a polymorphonuclear leukocyte (fig. 29). These foci showed considerable fibrin in their periphery and they were surrounded by loose edematous tissue composed of a few fibroblasts and many endothelial cells from the reticulum. There was some concentration of leukocytes about the periphery, gradually blending with the surrounding tissue. In the border and occasionally somewhat outside were small zones of endothelial cell increase surrounding cells of Langhan's type. The picture was that of an acute inflammatory reaction of the lymph node with small foci of necrosis and pus formation in which the endothelial leukocytes had a prominent part. Some of the areas showed greater density of the periphery than others, and in such the central leukocytic mass showed considerable fragmentation and necrosis.

COMMENT

The local, or what one might term the primary external, lesion in this disease has never been subjected to microscopic examination. As shown in case 4 and in other cases of tularemia, it is not necessary that a local lesion be formed. The organism can make its way through the unbroken skin and give rise to generalized symptoms with a primary adenopathy, or may gain entrance to the body producing symptoms of infection without either a local lesion or external adenopathy. From the standpoint of the number of days' duration of the disease the lesions shown in figure 28 are the earliest, but from the standpoint of the lesion itself one must assume that the lesion in the lymph node represented by figure 11 is equally early. Even these were probably preceded by small collections of leukocytes and epithelioid cells which have increased to a considerable extent in order to form even the small lesions of figures 28 and 11. A similar reaction is seen in figure 9, from the liver. In the early stages of the disease the reaction is as seen in figure 20 in which the reaction was definitely one of leukocytic response, the most marked increase or infiltration being of the epithelioid cells or histiocytes but including considerable numbers of lymphocytes and polymorphonuclears. Cells of Langhans' type apparently are formed relatively early in the process, and they were abundant in case 4 sixteen days after the onset. There was little evidence of fibrous tissue increase in the early lesion. It appeared definite in case 1 (fig. 1), but as though the process had just started. The duration of the lesions in this case was problematic. Opportunity for infection occurred about New Year's Day and the gland from which figure 1 was made was removed March 3. In this series of ten cases the longer the duration of the disease the greater was the amount of fibrosis produced about

the lesion. In case 1 death occurred three months and ten days after the first glandular enlargement was noticed, and the process showed a distinctly fibrous reaction about the lesions, quite a different picture from that seen in the biopsy material taken from case 1 nearly three months before. Cells of the Langhans' type were found about all lesions seen but were relatively more abundant about the less advanced ones.

The organisms or their products caused a profound reaction on the part of the endothelium of blood vessels and the histiocytes of the tissue, the latter being evidenced by large numbers of these cells present in the early lesions while the vascular change appeared as an obliterative endarteritis. Case 8 was of the longest duration, and figure 25 shows a lesion composed almost entirely of fibroblastic tissue in which nuclei are abundant. It is practically the same type as was seen in figure 22 with a somewhat shorter duration. It is interesting to note that the proportional number of fibroblast nuclei was considerably greater than in any other case, collagen being relatively scanty (figs. 21 and 22 should be contrasted). The lesions in this series of ten cases are similar and explainable on the basis of a common pathogenesis. It cannot be said, however, that lesions of the type portrayed and described here are sufficiently characteristic to make a diagnosis. They are similar to lesions seen occasionally in lymph node tuberculosis, but at least in this series they are of more uniform type than one would expect to find in a similar series of tuberculous cases. The finding of lesions similar or practically identical to those described should always lead to a suspicion of tularemia, and blood should be taken for agglutination reaction.

Several fatal cases have been reported in which no postmortem or antemortem examination was made. In some of these, symptoms indicating serious involvement of the lungs have been present. In addition, toward the end of life, there has been a more or less pronounced stupor. In the routine examination of autopsy tissues, the gross examination being performed by others, one of us found in a spleen section, typical nodules resembling those in the spleen and liver of case 1. The history revealed that the patient, a negro, had suffered for several months from a chronic swelling and suppuration of the axillary nodes, and finally had died after several days' stupor and other indications of meningeal involvement. The case was diagnosed, meningeal tuberculosis. There were symptoms of inflammatory activity in the lungs. At autopsy the lungs showed an acute bronchopneumonia, and one minute, apical, fibrous tubercle, largely hyalin. There was a tubercle with giant cell in the periphery. Otherwise, lesions suggestive of tuberculous involvement were not found. The spleen and liver showed numerous, opaque, rather firm nodules, which could be expressed whole from the surrounding tissue. The meninges were thickened and opaque over the lower portions of the brain. Microscopic examination showed a diffuse lymphocytic

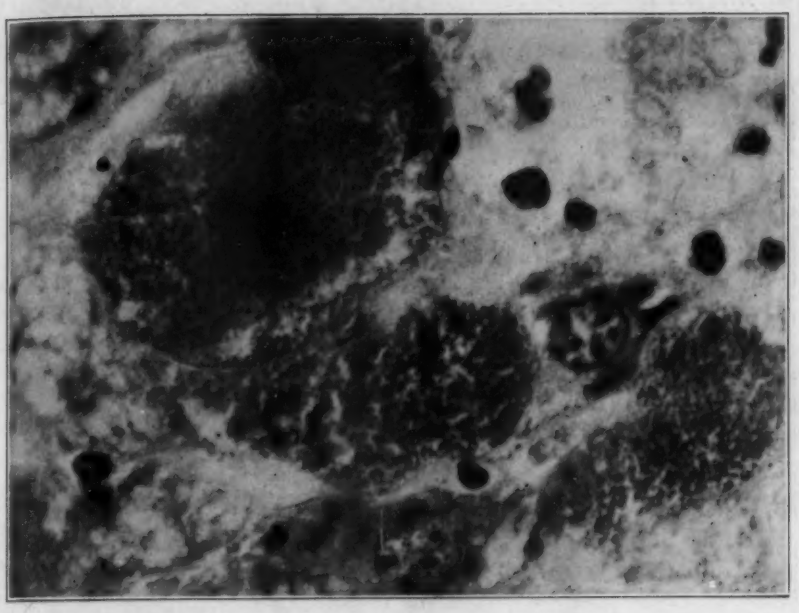

Fig. 30.—Bacterium tularense in cells of liver of mouse.

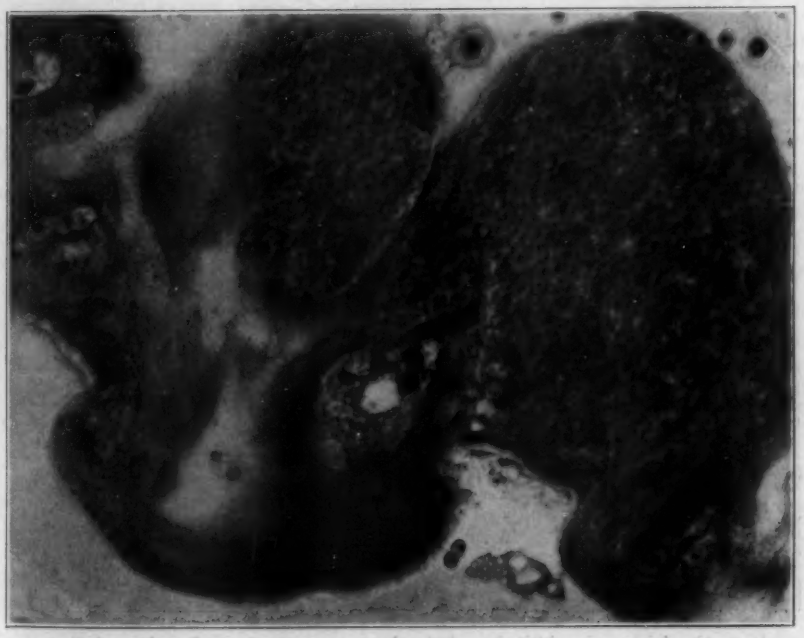

Fig. 31.—Bacterium tularense in epithelial cells of rectal sac of tick.

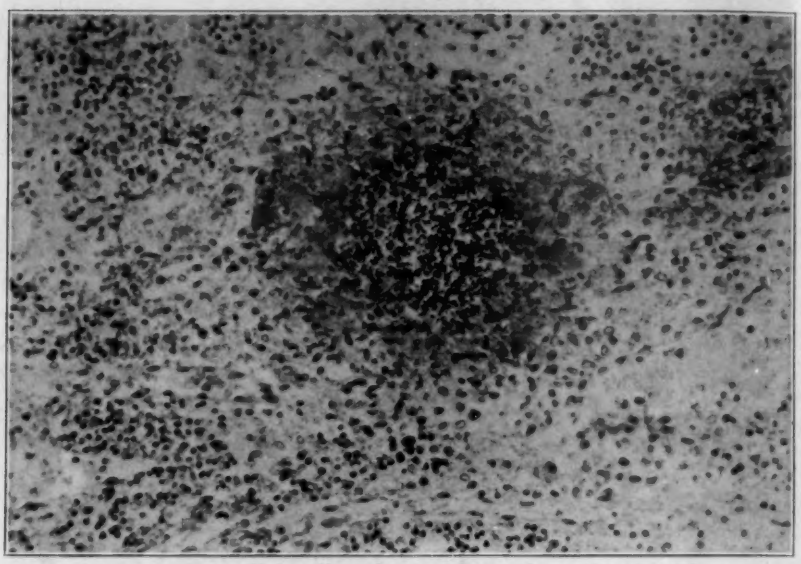

Fig. 32.—Lesions in spleen of guinea-pig killed four days after inoculation.

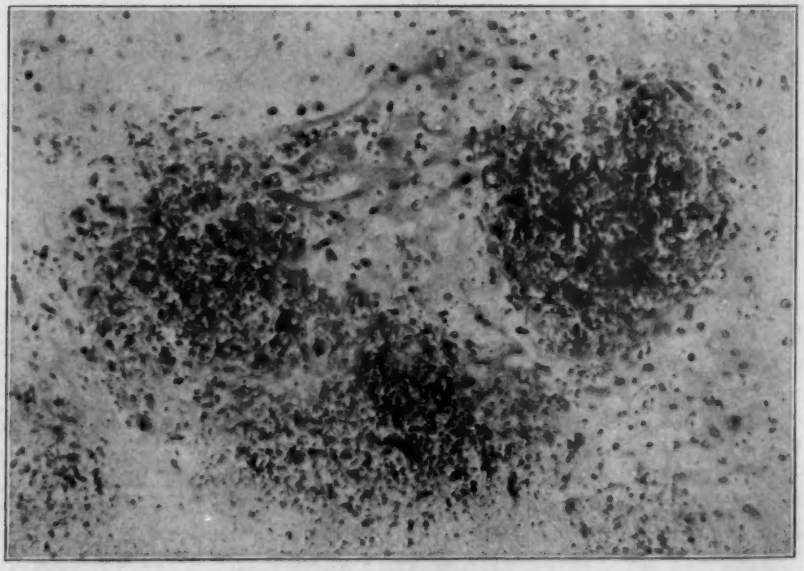

Fig. 33.—Liver of rabbit found dead on seventh day after inoculation.

infiltration with considerable thickening, and an occasional Langhans' cell surrounded by a few epithelioid cells. Some of the capillary vessels showed a proliferation of their endothelium. This lesion would be classed as a tuberculous meningitis and may have been. Tubercle bacilli could not be stained, but examination was not made of the blood and the tissues were not inoculated into pigs. Little evidence of active tuberculosis was found, though it was definitely searched for. This case is mentioned here with the hope that it may stimulate the examination of the brain in any future case; it suggests the possibility of a fatal termination of tularemia through meningeal involvement.

Comparative Pathology.—Bacterium tularense has been stained in sections of the lymph glands, spleen and liver (fig. 30) of the mouse; in sections of the lower intestine of the tick (fig. 31) and bed bug; in sections of the guinea-pig spleen, but not of the liver; in smears of the blood of the mouse, rat, rabbit and guinea-pig, and in the coelomic fluid of the tick and bed bug; in smears of the spleen of the mouse, rat, rabbit and guinea-pig, but smears of a typical spleen of a guinea-pig or rabbit may not show any organism; in smears of the liver of the mouse and rat, and in smears of the lymph glands of the guinea-pig. The white mouse is the animal of choice for ready demonstration of the organism in smears and sections, and for constancy of cultivation of the organism from the heart blood.

The pathologic condition in naturally infected ground squirrels and in experimental animals has been covered in papers previously published, references to which are given.[9] The lesions in the less resistant laboratory animals resemble the early lesions in man, but the reaction is more intense. The mouse is extremely susceptible, and the tissues are diffusely affected. *Bacterium tularense* is found in enormous numbers in both hepatic and Küpfer cells (fig. 30). The opossum and guinea-pig (fig. 32) give similar reactions with focal lesions. The rabbit is somewhat more resistant (fig. 33). The animals so far used have not developed the fibrous tissue proliferative changes seen in man. Langhans' cells are seen occasionally in guinea-pig lesions.

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IMMUNE REACTIONS IN TISSUE CULTURE I

REACTION OF LUNGS FROM NORMAL AND IMMUNIZED RABBITS TO PIGEON ERYTHROCYTES *

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INTRODUCTION

Since the early experiments of Metchnikoff,[1] the question of the relation of various groups of cells in the animal organism to immunity production and to the various immune phenomena, such as anaphylaxis, has attracted the attention of great numbers of investigators. As successive new factors in the immune processes were demonstrated, the school of Metchnikoff continued on the basis of great numbers of experiments to ascribe to the phagocytic cells—the macrophages or, as they are called today, histiocytes—the primary and practically the only rôle in the immune reactions. With the discovery of the immune bodies and complement in the blood serum a long controversy ensued over the site of origin of these blood antibodies and the relative importance of the humoral versus the cellular elements in immunity. Metchnikoff and his students continued to derive the blood antibodies—their cytases—from the phagocytic cells; they claimed that these substances were absent from native plasma but were liberated from the leukocytes, which they identified in part with macrophages destroyed during the process of clotting. Today a compromise view is widely advocated (Zinsser,[2] Aschoff[3]). In this opinion the site of antibody formation is believed to be the system of histiocytes, and the presence of these substances in the blood stream is taken to be either an excess or a mobilization of antibody.

Proof for the origin of antibodies in those organs and tissues liberally supplied with phagocytes has been amply provided in the experiments of Metchnikoff. Cary[4] and Motohashi[5] also have contributed important experimental data supporting this theory. Further evidence for the

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* From the Department of Anatomy, University of Chicago, Chicago.

* This work has been conducted under a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago. The cost of publishing the colored plate has also been met by the foundation.

1. Metchnikoff, E.: L'immunité dans les maladies infectieuses, Paris, Masson, 1901.

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5. Motohashi, S.: J. M. Research **43**:419 and 473, 1922.

participation of the system of histiocytes in antibody formation may be obtained from those experiments in which antibody formation is studied in animals in which the histiocytes have been "blockaded" with the colloidal vital dyes and other colloids. Particularly noteworthy in this field are the experiments of Murata,[6] Bieling and Isaac,[7] Jungeblut and Berlot,[8] Gay and Clark,[9] Stewart and Parker[10] and many others who have reported more or less depression of antibody formation in "blockaded" animals. While some investigators, as Rosenthal[11] and his co-workers and Lewis and Loomis,[12] have found that vital staining does not affect the immune body production, the greater part of the evidence in hand favors the former view.

What cells are to be considered as histiocytes or reticulo-endothelial elements? As these cells are frequently not clearly differentiated from common vascular endothelium, and in view of the evidence quoted above in favor of the participation of the histiocytes in immunity production, it is necessary to compare these two groups of cells. Maximow,[13] in a long series of articles, has reported observations on the reactions of endothelium during embryonic life, in various inflammatory conditions and in tissue culture. As the result of his studies he differentiates sharply between reticulum endothelium and vascular endothelium. The latter he believes, in the adult, to be a highly differentiated cell type which has but limited possibilities for further development except into fibroblasts.

Marchand[14] and his pupil, Georg Herzog,[15] believe that the common vascular endothelium is one of the sources of the so-called "Marchand's adventitial cells;" these, as Maximow has shown, are identical with his resting wandering cells and, implicitly, with the histiocytes in general. Marchand and Herzog accordingly ascribe to vascular endothelium the potency of producing histiocytes. Furthermore, the adventitial cells, according to Marchand and Herzog, are supposed to be able also to form

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14. Marchand, F.: Handb. d. allg. Path. **4**:78, 1924.

15. Herzog, G.: Beitr. z. path. Anat. u. z. allg. Pathol. **61**:325 and 377, 1915; Klin. Wchnschr. **2**:684, 1923.

white blood cells. The endothelium, then, is considered by the school of Marchand to be able to form directly, and indirectly by way of the adventitial cells, on the one hand granular leukocytes, and on the other hand mononuclear wandering inflammatory cells, which have been variously labelled as the polyblasts by Maximow, cellules rhagiocrines by Renaut,[16] macrophages by Metchnikoff and Evans,[17] histiocytes by Aschoff and Kiyono [18] and clasmatocytes by Sabin.[19]

By means of the method of vital staining introduced by Ribbert [20] and extensively developed by Goldmann,[21] Aschoff and Kiyono, Tschaschin [22] and Evans, the common vascular endothelium can be sharply distinguished from reticulum endothelium by the failure of the former to store the dyes or at best to store them but slightly. The cells lining the vascular spaces in the spleen and the lymph channels in the lymph nodes are considered by many authors as being quite different from vascular endothelium and hence the name litoral cells has been applied to them. The intimate relationships between these litoral cells and the reticulum cells of the hemopoietic organs are beautifully pictured by Downey.[23] By means of his careful histologic technic he was unable to distinguish these litoral cells from the reticulum cells. By the same method he showed distinct differences between vascular endothelium and the reticulum or specific endothelium—that is, the litoral cells. Maximow also believes that the litoral cells are merely histiocytes lining blood or lymph channels. He showed, too, that true endothelium behaves in tissue culture quite differently from the histiocytic litoral cells, and therefore, Maximow denies the origin of adventitial cells from common endothelium.

Certain investigators using colloidal carbon (Higgins' India Ink) intravenously, as Foot,[24] Permar,[25] McJunkin [26] and Fritz Herzog,[27] claim that vascular endothelium, because of its ability to take carbon and transform itself into ameboid phagocytic cells, should be included in the histiocytic system. Using this test they would include particularly the pulmonary capillary endothelium. While the final opinion has not been

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16. Renaut, J.: Arch. d'anat. micr. **9**:495, 1907.
17. Evans, H.: Am. J. Physiol. **37**:243, 1915.
18. Aschoff, L.: Verhandl. d. deutsch. path. Gesellsch. **16**:107, 1913.
19. Sabin, F. R.; Doan, C. A., and Cunningham, R. S.: Contrib. Embryol., Carnegie Inst., Washington **16**:127, 1925.
20. Ribbert, H.: Ztschr. f. allg. Physiol. **4**:20, 1904.
21. Goldmann, E. E.: Beitr. z. klin. Chir. **64**:192, 1909.
22. Tschaschin, S.: Folia haemat. **17**:317, 1913.
23. Downey, Hal.: Haemotologica **3**:1, 1922.
24. Foot, N. C.: Anat. Record **30**:15, 1925.
25. Permar, H.: J. M. Research **42**:209, 1921.
26. McJunkin, F. A.: Am. J. Anat. **25**:27, 1919.
27. Herzog, F.: Ztschr. f. d. ges. exper. Med. **43**:79, 1924.

reached on the question of the storage of colloidal carbon by capillary endothelium, the experiments of Stillwell [28] throw much light on the subject. This investigator, examining the vessels of the tongue of the living frog, into the dorsal lymph sac of which colloidal carbon had been injected, found that the carbon in the endothelial cells was soon given over directly to the adjacent adventitial histiocytes. Similar observations were reported by Lang.[29] According to this view, the experiments of Foot, Permar and F. Herzog are to be so interpreted that the carbon-containing phagocytes are not of endothelial but of histiocytic or adventitial cell origin.

At the suggestion of Dr. A. Maximow I repeated the work of Oeller,[30] who claimed to have found a marked myelopoietic activity on the part of pulmonary capillary endothelium in guinea-pigs which were thrown into anaphylactic shock by a second injection of chicken erythrocytes. His results, as applicable to the lungs, have been denied by Schilling,[31] Seemann,[32] and Gerlach and Finkeldey,[33] who have repeated his experiments. I have also repeated his experiments, and my observations with respect to the lungs are quite at variance with his. The details of these experiments cannot be given here. I found the pulmonary capillary endothelium to be inactive, and agree entirely with Schilling, Seemann and Gerlach and Finkeldey. Siegmund [34] and Domagk,[35] however, have reported interesting changes in the capillary endothelium of the lungs in animals in certain anaphylactic and other immune processes. The latter explains the asphyxial symptoms in anaphylaxis as due to a marked swelling of the pulmonary capillary endothelium.

Because of these facts and in view of the complicated histology of the lung, it occurred to me that some light might be thrown on this unsettled problem in particular and possibly on immune reactions in general, if I would culture tissues from normal, sensitized and immunized animals and then add the antigen in vitro to the several sets of explants. In a thorough search of the literature it was impossible to find reports of such experiments. My purpose, therefore, was to culture lungs and other tissues, from immunized and control animals and then to add to these explants an antigen such as pigeon erythrocytes. The latter was

28. Stilwell, F. E.: Folia haemat. **33**:76, 1926.

29. Lang, F. J.: Rôle of Endothelium in the Production of Polyblasts in Inflammation, Arch. Path. **1**:41 (Jan.) 1926.

30. Oeller, H.: Krankheitsforschung **1**:47, 1925.

31. Schilling, V.: Deutsche med. Wchnschr. **51**:25, 1925.

32. Seemann, G.: Beitr. z. path. Anat. u. z. allg. Pathol. **74**:345, 1925.

33. Gerlach, W., and Finkeldey, W.: Verhandl. d. deutsch. path. Gesellsch. **22**:173, 1926.

34. Siegmund, H.: Verhandl. d. deutsch. path. Gesellsch. **20**:260, 1925.

35. Domagk, G.: Verhandl. d. deutsch. path. Gesellsch. **20**:280, 1925.

decided on because of my previous in vivo work with this antigen and because of the visibility and distinctiveness of these cells.

Although previous experiments along this line in tissue culture were not reported in the literature, some interesting observations on this point were made by Briscoe.[36] This investigator introduced chicken erythrocytes and certain bacteria into the lungs, by way of the trachea, of normal guinea-pigs as well as such as had been immunized against these antigens. He found quite regularly that in the first twenty-five hours there was little phagocytosis of the foreign red cells in the normal animals but that phagocytosis was rapid and marked in those animals which had been immunized, or which received immune serum subcutaneously at the time the erythrocytes were introduced, or which received erythrocytes treated with immune serum. He found, moreover, that the addition of inactivated serum to the red corpuscles was just as effective in producing phagocytosis as normal immune serum. His results will be discussed below in the consideration of my own observations.

Shortly after Carrel had worked out his method of tissue culture on the basis of Harrison's [37] earlier work, Carrel and Ingebritsten [38] showed conclusively that lymph node and bone marrow of the guinea-pig in tissue culture respond to the presence of goat erythrocytes by the formation of an antibody (hemolysin) against them. The liquid extracted by freezing and thawing from these cultures withstood heating to 56 degrees and caused hemolysis if complement was added. In these experiments they noticed that the leukocytes of the explant began to phagocytize the foreign erythrocytes, beginning with the third day, and that hemolysin could be extracted from the cultures after the fourth or fifth day.

Soon after these experiments were reported, Przygode [39] showed that the spleen of the rabbit responds to the presence of horse serum in tissue culture by the formation of precipitin against this antigen, and to typhoid bacilli by the production of agglutinin for this organism. He believed that the mobile white blood corpuscles and the endothelium of the spleen partake in immunity formation.

Tissue cultures were also made use of for slightly different immunologic purposes by Foot,[40] Hadda and Rosenthal,[41] Lambert [42]

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36. Briscoe, J. C.: J. Path. & Bact. **22**:66, 1908.

37. Harrison, R. G.: Proc. Soc. Exper. Biol. & Med. **4**:140, 1907.

38. Carrel, A., and Ingebritsten, R.: J. Exper. Med. **15**:287, 1912. Carrel, A.: Berl. klin. Wchnschr. **49**:533, 1912.

39. Przygode, P.: Wien. klin. Wchnschr. **26**:841, 1913; **27**:201, 1914.

40. Foot, N. C.: Centralbl. f. allg. Pathol. u. path. Anat. **23**:578, 1912.

41. Hadda, S., and Rosenthal, F.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **16**:526, 1913.

42. Lambert, R. A.: J. Exper. Med. **19**:277, 1914.

and Lambert and Hanes.[43] These investigators showed that various tissues would not grow or at best would grow but slightly in cultures made with plasma from animals which had been immunized against these particular tissues. Fischer [44] has published some observations on the rate of growth of chicken fibroblasts in cultures containing a foreign protein such as dog serum. He has shown that the cultures acquire a tolerance for dog serum so that after a time they can live in a concentration of the serum which is toxic for nontreated control cultures. He regards this reaction as being possibly of an anaphylactic or immune nature. Kuczynski, Tenenbaum and Werthemann [45] were unable to detect hemolysin formation against sheep cells by rabbit spleen cultures. It is to be noted, however, that in these experiments only the serum from the cultures was tested for hemolysin, whereas in the experiments of Carrel and Ingebritsten hemolysin was extracted from the cultures by freezing and thawing.

Cultures of the lung have been carried out by Awrorow and Timofejewski,[46] Mitsuda,[47] Timofejewski and Benevolenskaya,[48] Lang [49] and Carleton.[50] Timofejewski and Benevolenskaya regard the numerous phagocytic cells in the cultures as derivatives of the alveolar epithelium. Carleton derives the great majority of the alveolar phagocytes from the alveolar epithelium; a few he believes come from the mononuclear cells of the blood and the peribronchial and perivascular histiocytes. Lang has studied lung cultures of the rabbit in great detail. He traces the alveolar phagocyte to his septum cells. The latter he believes are partially differentiated mesenchymal elements within and on the alveolar walls, which under such stimuli as bacteria or dust particles or explantation develop into alveolar phagocytes. He believes, moreover, that epithelium is present in the alveoli only in the shape of nonnucleated plaques.

It is unnecessary to go into the voluminous literature dealing with the alveolar phagocyte, including in this term the dust cells and the Herzfehlerzellen. The question has been reviewed thoroughly by Briscoe and Aschoff and most recently by Lang. My studies, to be

43. Lambert, R. A., and Hanes, F. M.: J. Exper. Med. **13**:495, 1911.

44. Fischer, A.: Tissue Culture: A Text Book, Copenhagen, Levin & Munksgaard, 1925.

45. Kuczynski, M.; Tenenbaum, E., and Werthemann, A.: Virchow's Arch. f. path. Anat. **258**:687, 1925.

46. Awrorow, P. P., and Timofejewski, A. D.: Virchow's Arch. f. path. Anat. **216**:184, 1914.

47. Mitsuda, T.: Virchow's Arch. f. path. Anat. **242**:310, 1923.

48. Timofejewski, A. D., and Benevolenskaya, S. W.: Virchow's Arch. f. path. Anat. **255**:613, 1925.

49. Lang, F. J.: Arch. exper. Zellforsch. **2**:93, 1926.

50. Carleton, H. M.: Phil. Trans. Roy. Soc., series B, **213**:365, 1925.

described below, fully corroborate the observations of Lang. In agreement with him, I consider that the cells in my lung cultures are mesenchymal in origin and I shall speak of them as phagocytes or histiocytes.

METHOD

For the foregoing reasons, pigeon erythrocytes were the antigen in the following experiments which were carried out on five treated and eight normal or control rabbits. Two of the rabbits received intravenously two weeks before explantation the red blood cells of 3 cc. of pigeon blood, washed three times in 0.85 per cent salt solution. One rabbit received a similar injection of erythrocytes four weeks before explantation. Two of the rabbits each received two injections of the same dosages with eight day intervals, the last injection being two weeks before explantation. Immediately after the second injection of erythrocytes, these two animals were prostrated for several hours; they seemed to have passed through a definite anaphylactic shock. The erythrocytes used in all of the immunization procedures and in the cultures were always taken from the bottom of the red cell layer of the centrifugalized blood, and were accordingly unlikely to be mixed with thrombocytes which settle, on centrifugalizing, in the buffy coat.

The explantation technic was that in general use in Maximow's laboratory.[51] After the cultures were allowed to grow for several days they were washed in Ringer's solution to remove most of the serum from the explants, as rabbit serum usually contains hemolysin for pigeon erythrocytes. To these washed cultures was added a drop of a suspension of one part of washed pigeon erythrocytes to twenty parts of bone marrow or embryonic extract. These extracts did not hemolyze or agglutinate the pigeon red cells. Except for the periods when they were under the microscope, the slides with the cultures were kept inverted so that the bit of tissue rested on the cover slip and the liquids of the culture were above the tissue. This was of particular importance in the experiments because it insured the contact of the heavy foreign erythrocytes with the bit of lung tissue. This would obviously not obtain in a hanging drop culture, because the heavy nucleated pigeon erythrocytes would sink to the bottom of the drop and would therefore not be in contact with the cells of the culture. After the addition of the erythrocytes, the cultures were carefully observed in the living condition. They were then fixed in Zenker-formalin at different stages, embedded in celloidin, cut in serial sections after the method of Maximow and stained with dilute Delafield's hematoxylin and eosin-azure II.

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51. Maximow, A. A.: Ztschr. f. wissensch. Mikr. **26**:177, 1909; Arch. f. mikr. Anat. **96**:494, 1922; J. Infect. Dis. **24**:549, 1924.

RESULTS

(*a*) *Lungs of Normal Rabbits in Tissue Culture.*—The description of the growth of rabbit lung in tissue culture as given by Lang also holds for my observations on the growth of lungs from normal control rabbits as well as those which had previously been injected with pigeon erythrocytes. The lungs from the variously treated animals presented similar pictures. On the first day after explantation a rapid migration of fair numbers of small cells was seen in the fibrin surrounding the explant. These cells, as seen in the living condition, consisted for the most part of polymorphonuclear (special) leukocytes and some small mononucleated cells. The latter had small pointed pseudopodia of hyalin cytoplasm and were almost entirely filled with a homogeneous nucleus. They were small and medium sized lymphocytes and migrated into the fibrin from the vessels and lymphoid collections of the lung. They showed considerable variations in number in individual cultures. After the first day larger cells in greater and greater numbers appeared in the fibrin; these cells were four and five times the size of the lymphocytes, they had many filiform or membrane-like pseudopodia and the cytoplasm was finely vacuolated. According to Lang they are to be looked on as mobilized phagocytes in part ready in the wall and in part originating from embryonic connective tissue in the septums. The nucleus was small when compared with the cytoplasm. As the explant developed, the small cells, both granular and nongranular, disappeared either by lysis or phagocytosis by the large cells or both. After the first washing, which occurred on the third or fourth day, the culture consisted almost entirely of the original explant which was surrounded by tremendous numbers of large cells. There was usually, by this time, a fair degree of liquefaction of the fibrin. This occurred particularly when small bits of bronchi were contained in the explant. If the bronchus was situated at the edge of the bit of tissue, the cilia could be seen to beat for many days. After washing the cultures, pigeon erythrocytes were added as described previously.

Immediately after adding the red blood cells certain gross differences were seen in the normal and the immune cultures. In the former the erythrocytes were present as a fairly homogeneous slightly red opaque suspension. In the latter, however, the red cells were rapidly agglutinated into clumps so that they presented the typical "brick dust" appearance of agglutinated erythrocytes. Differences were not observed in the ability to agglutinate the red cells in the cultures taken from those rabbits which had previously received one injection of pigeon cells and those which had received two injections.

(*b*) *Normal Rabbit Lung Cultures and Erythrocytes (Living Cultures).*—The erythrocytes settled singly or in various sized clumps about the bit of tissue in the explant. After several hours they were

seen clustering about the large phagocytes which were so extremely numerous in rabbit lung cultures. I did not see the phagocytes actually move toward the red cells. My impression of this process of clustering was that the erythrocytes which were distributed evenly over the surface of the explant came in places in direct contact with the phagocytes. This was particularly true of those areas in which the fibrin had been liquified. After the first ten or twelve hours the red corpuscles had assumed a fairly constant position about the phagocytes. They were usually radially arranged about these cells, much in the manner of the petals of a daisy, the long axis of the large nucleated erythrocytes being perpendicular to the tangential surface of the phagocytes. The erythrocytes were definitely adherent to these cells, as could be shown by tilting one side of the culture slide. In this case the erythrocytes moved slightly in the current of liquid but did not sever their attachments to the phagocytes. In but few of the phagocytes from seven normal animals were there any ingested erythrocytes. As the cultures were allowed to develop the foreign erythrocytes showed a gradually increasing hemolysis, so that after three days practically all of the red cells were laked. In these the nuclei were prominent, highly refractile and surrounded by a colorless zone of cytoplasm which would have been imperceptible but for the light gray contour of the shadow cell. These cells were also much smaller than the fresh hemoglobin containing erythrocytes. Some of the cultures were continued for as long as twelve days. In these, in spite of the high grade clumping of the red cells about the phagocytes there was no phagocytosis. This process was all the more striking, in that one received the impression after looking at these cultures that there was a definite force attracting the erythrocytes to the phagocytes and holding them there.

To some cultures from normal rabbits, pigeon erythrocytes were added on explantation immediately after the clotting of the plasma, because the liquid plasma of the rabbit completely hemolyzes pigeon erythrocytes during the process of clotting. These cultures were watched for as long as a week and phagocytosis was not seen in them. At this time they were opened and another drop of fresh erythrocytes in bone marrow or embryonic extract, both with and without washing the cultures, was added. These cultures were followed for another week; they failed in this period to show phagocytosis of the erythrocytes.

Seven of the eight control animals showed a practically identical reaction. This, as described above, is characterized by a marked grouping of the erythrocytes about the phagocytes and the consistent failure of the latter to ingest the red blood cells. One of the control lungs was diffusely contaminated. These cultures all showed a high grade of phagocytosis. In contrast to this is the fact that the occasional occurrence of contamination in cultures from the seven other control lungs

seemed not to play any rôle in the phagocytosis of the pigeon erythrocytes. (This will be discussed later after the study of the fixed and stained material has been described.)

(*c*) *Lungs from Immunized Rabbits and Erythrocytes (Living Cultures).*—These cultures, parallel with those from the control rabbits, received the erythrocytes after several days' growth in vitro and after being washed. When examined under the microscope one half hour after the addition of the red cells, the latter were seen in clumps of varying size against the bits of tissue and the phagocytes free in the fibrin. Isolated erythrocytes in groups of two or three were also to be seen lying free or in proximity to the phagocytes. After two hours, large numbers of histiocytic phagocytes had ingested the foreign cells. The histiocytes then had quite a different appearance. Instead of their slightly irregular shape and finely vacuolated cytoplasm and distinct membrane-like pseudopodia they became distinctly rounded, the pseudopodia had disappeared for the most part and the cytoplasm was filled with bright golden and in places orange circular or slightly oval disks in which any suggestion of a nucleus was not to be seen as a rule. The foreign erythrocytes which were free in the culture were usually pale yellow and distinctly oval; their color was red when large numbers of them were massed together. When ingested, however, the color of the erythrocytes changed and became definitely golden. The red cells were much smaller after being phagocytized, and one got the impression that they had become spherical and shrunken in the body of the phagocyte.

After four hours, the degree of phagocytosis was marked. After eighteen hours, the process seemed to have reached its climax, and practically all of the cells in contact with the pigeon red cells had ingested the latter. However, in most of the cultures there were some phagocytes in contact with erythrocytes which did not show any tendency toward phagocytosis. Reasons for this were not found in studying the cultures. Moreover, there were marked differences in the degree of phagocytosis exhibited by various cultures from the same and different animals. Some of these were due to variations in distribution of the phagocytes, in the degree of liquefaction of the fibrin and in the distribution and agglutination of the erythrocytes. There were probably other factors determining the differences in degrees of phagocytosis; these will be considered later. As a general rule, the phagocytosis was carried on to a greater extent by those phagocytes which were close to the explant than by those which had migrated out into the fibrin. This point could not be determined with exactness in the living cultures because it was difficult to tell whether phagocytes filled with erythrocytes were hidden by an opaque red mass of agglutinated erythrocytes. However, the high grade phagocytosis by histiocytes close to the explant could be seen easily in those areas in which liquefaction of the fibrin allowed the red cells to come in immediate contact with the phagocytes.

In two rabbits, a control and one which had received pigeon erythrocytes two weeks before explantation, the attempt was made to remove the blood from the lungs. This was tried in the following manner. In each case the branch of the pulmonary artery going to the right lung was ligated and portions of the lung (from each animal) were then removed under sterile precautions for explantation. Sterile Ringer's solution was then perfused through the left lung of each animal by means of a cannula in the left pulmonary artery. This was continued until the perfusate from the left ventricle of the heart was clear. The lungs became clear white on the surface; when incised they showed a slightly pink color. Portions of the lungs were then removed from each animal for explantation. In neither of the perfused lungs, as seen under the microscope, had I been able to remove all of the red blood cells from the vessels. Differences had not been found between the perfused and nonperfused lungs of the same animals, with respect to their reactions to the pigeon cells.

In the cultures from the five rabbits which previously had been injected with pigeon erythrocytes, differences could not be seen in the living cultures between those which had received one and those which received two injections of the erythrocytes. The exception to this was one rabbit which had received one intravenous injection of erythrocytes four weeks before explantation. The cultures from this animal behaved as though they came from an untreated control in that they practically did not contain any cells which phagocytized the red cells. The serum from this animal was not titrated for its antibody content. When the erythrocytes were added to these cultures there was a marked agglutination of the red cells comparable to that found in the other immune cultures.

(*d*) *Addition of Immune Serum to Normal Lung Cultures Plus Erythrocytes (Living Cultures).*—A series of experiments was carried out to determine the effect of the addition of antipigeon erythrocyte rabbit serum to cultures from normergic rabbit lungs in which phagocytosis had not been seen to occur. In these experiments lung cultures were selected which had received one or two drops, at intervals, of pigeon red cells and had failed to phagocytize them in periods as long as twelve days. When examined under the microscope all of these cultures had a definitely characteristic appearance. Large numbers of pigeon erythrocytes were clumped about most of the free phagocytes and were adherent to them as described previously. Most of the red cells were shadow cells, the nuclei being, however, conspicuous. Such cultures were opened, and one drop of antipigeon erythrocyte rabbit serum with a titration of 1 to 3,000 for agglutinin, diluted 1 to 30 was added. The cultures were then sealed and observed. Similar cultures were likewise

treated with a drop of 1 to 30 normal rabbit serum which did not contain any agglutinin for pigeon erythrocytes. These cultures also were carefully observed in the living condition under the microscope. A change was not observed in the relation of the phagocytes to the surrounding erythrocytes in those cultures which received the diluted normal serum. Those cultures, however, to which the diluted immune serum had been added showed a striking picture. The following is a typical experiment. The culture was kept under the microscope at 37 C. and carefully watched immediately after the immune serum was added. Changes in the position or condition of either the erythrocytes or the phagocytes were not seen until twenty-five minutes after the addition of the serum. At this time the picture had changed as if by magic. The daisy-like arrangement of the red cells without the phagocytes suddenly began to disappear. The red cells were now seen to be within the phagocytes. The actual process of phagocytosis was difficult to follow. Here and there an erythrocyte was seen to be included between two thin, barely perceptible pseudopodia, and then suddenly the free ends of the pseudopodia had fused, the phagocyte shortened somewhat in this diameter and the erythrocyte was within the histiocyte. When phagocytosis started it was extremely rapid and extensive, so that in a few minutes a cell which had previously been seen to be surrounded by erythrocytes suddenly contained twenty or thirty red cells. A similar set of experiments was carried out by adding the dilute immune serum, with a drop of fresh erythrocytes, to normal cultures which had failed to phagocytize the erythrocytes previously added to them. Here the pictures were even more striking, the phagocytes took up, apparently with equal facility, the fresh hemoglobin containing erythrocytes and the old hemolyzed shadow cells (fig. 6). The phagocytosis was carried on by practically every phagocytic cell in contact with erythrocytes, irrespective of its location in the cultures; that is, whether it was free in the explant or free in a liquefied area, or adherent to the surface of the original bit of tissue.

Similar experiments were carried out using the immune serum, from the same animal, which had been inactivated by heating at 56 to 58 C. for thirty minutes. When this inactivated serum was added to cultures, the same phenomenon was observed as in those cultures receiving the untreated immune serum, the resultant phagocytosis was just as prompt in appearance and just as intensively widespread.

(*e*) *Lymphoid Tissue and Erythrocytes* (*Living Cultures*).—As further control experiments, with the purpose of reaching a better understanding of the inability of the normal lung phagocytes, in tissue culture, to ingest the foreign erythrocytes, the following experiments were carried out. Small pieces of rabbit mesenteric lymph node were explanted in the same manner as was done with lungs. Washed pigeon erythrocytes were added to some of these immediately after the fibrin

of the culture had clotted. These cultures were then observed for several days. In them there was a great outwandering of lymphocytes which died in the course of the first few days. The pigeon red cells hemolyzed and began to disintegrate after several days. I was unable to obtain any information from these cultures. Other cultures of normal rabbit lymph node were grown for three days and then washed in Ringer's solution. This removed the great numbers of disintegrating lymphocytes and exposed quite clearly large numbers of histiocytic cells about the explant. These cultures then received a drop of pigeon erythrocytes in embryonic extract. After a few hours, the red cells began to cluster about the phagocytes. By the end of ten hours, it was hardly possible to delineate the outlines of the phagocytes because of the large numbers of erythrocytes clustered about them. These were packed so closely that it was difficult to see the outlines of the individual red cells; they constituted a distinctly red, irregular halo about the phagocytes. As seen in the living condition, these phagocytes seemed identical in appearance with those observed in the lung cultures. By the end of twenty-four hours many slightly larger phagocytes began to appear at the edge of the explant. These cells frequently contained bright yellow granules which were considered to be waste pigment. These areas were observed carefully, and as the hours passed phagocytes containing erythrocytes began to appear in the fibrin about the explant. In most cases one was impressed with the fact that the red cell-containing phagocytes had wandered away from the explant after having taken up the erythrocytes. These erythrocyte-containing histiocytes were comparatively easy to follow, because they usually contained much waste pigment which was so plentifully present in the reticulum cells of the explant. Some of the cells, after ingesting the red cells, were seen to glide away slowly from the explant. It was curious to see how far some of the cells could move from the explant and still remain attached to it by thin streamers of protoplasm.

(*f*) *Summary of the Results Obtained from the Living Cultures.*—There is, then, a marked attraction manifested by the histiocytes of normal lung and lymph node for pigeon erythrocytes in tissue culture. This is shown by the clumping about and the adherence to the surface of the phagocytes by the red cells. The phagocytes from the normal lungs rarely ingest the foreign erythrocytes, while the pigment containing phagocytes in the lymph node cultures phagocytize large numbers of the pigeon cells. The smaller histiocytes in lymph node cultures seldom ingest the foreign cells; they behave very much like the phagocytes in cultures from normal lungs. The phagocytes in cultures of lungs from immunized rabbits ingest the foreign erythrocytes rapidly and in great numbers. The rate of phagocytosis was decidedly faster, in my experiments, in the immunized lung cultures, than in those from normal node.

All illustrations were drawn with the aid of a camera lucida. Bausch and Lomb 1.9 mm. objective and × 10 ocular.

Explanation of Plate 1

Fig. 1.—Phagocytes of lung culture from an immunized rabbit filled with erythrocytes; five days in vitro; erythrocytes added twenty-six hours previously.

Fig. 2.—Lymph node culture of normal rabbit, at the left of the cut is the margin of the explant showing mature histiocytes filled with waste pigment, the right side of the figure shows one large histiocyte filled with erythrocytes and many smaller phagocytes surrounded by erythrocytes; five days in vitro; erythrocytes added thirty-six hours previously.

Explanation of Plate 2

Fig. 3.—Normal lung culture; phagocytes surrounded by erythrocytes; no evidence of phagocytosis; four days in vitro; erythrocytes added twenty hours before fixation.

Fig. 4.—Normal lung culture; laking of erythrocytes but no phagocytosis; this is a typical arrangement of the red cells about the phagocytes in lung cultures, five days in vitro; erythrocytes added forty-eight hours before.

Fig. 5.—Normal lung culture; three days in vitro; erythrocytes added six hours previously.

Fig. 6.—Phagocyte from normal lung culture; fixed one hour after the addition of immune serum; erythrocytes added on explantation and again with the immune serum; the cell contains the old hemolyzed erythrocytes (*Oerc*) and the fresh red cells (*Ferc*); the latter are undergoing granular degeneration of the hemoglobin; at the upper pole an erythrocyte is partially inclosed in the cell; fixation probably occurred during phagocytosis, six days in vitro. Ocular 18 and 1.9 mm. Bausch and Lomb objective.

Explanation of Plate 3

Fig. 7.—Phagocytes filled with erythrocytes in lung culture from immunized rabbit; three days in vitro; erythrocytes added six hours before fixation.

Fig. 8.—Phagocyte from lung culture of a normal rabbit showing low grade phagocytosis which occurs in some lung cultures; the cell contains the residue of three pigeon red cells; four days in vitro; erythrocytes added twenty hours previously.

Fig. 9.—Phagocytes from immune lung culture; the erythrocytes within the phagocytes show a diffusion of chromatin through the cytoplasm; there is also a mitotic figure in one of the phagocytes which contains two erythrocytes; three days in vitro; red corpuscles added six hours before fixation.

Fig. 10.—Small histiocyte from culture of normal lymph node; this shows the great accumulation of pigeon cells about the phagocyte; five days in vitro; pigeon erythrocytes added thirty-six hours previously.

Fig. 11.—Characteristic grouping of erythrocytes about a phagocyte in lung culture from normal rabbit; distinctly fewer red cells about this phagocyte than in the one from the lymph node shown in figure 10; four days in vitro; erythrocytes added thirty hours previously.

PLATE 1

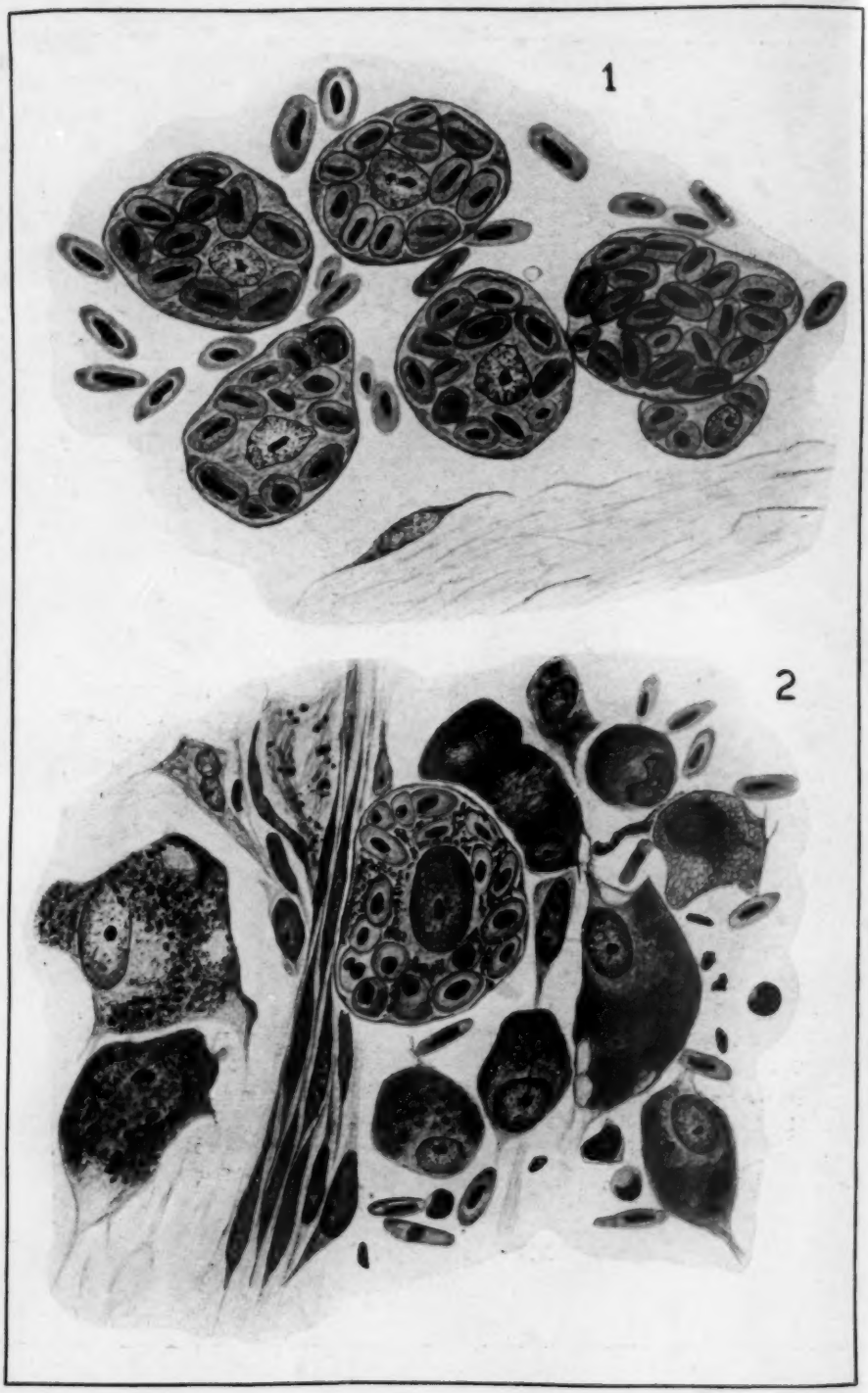


PLATE 2

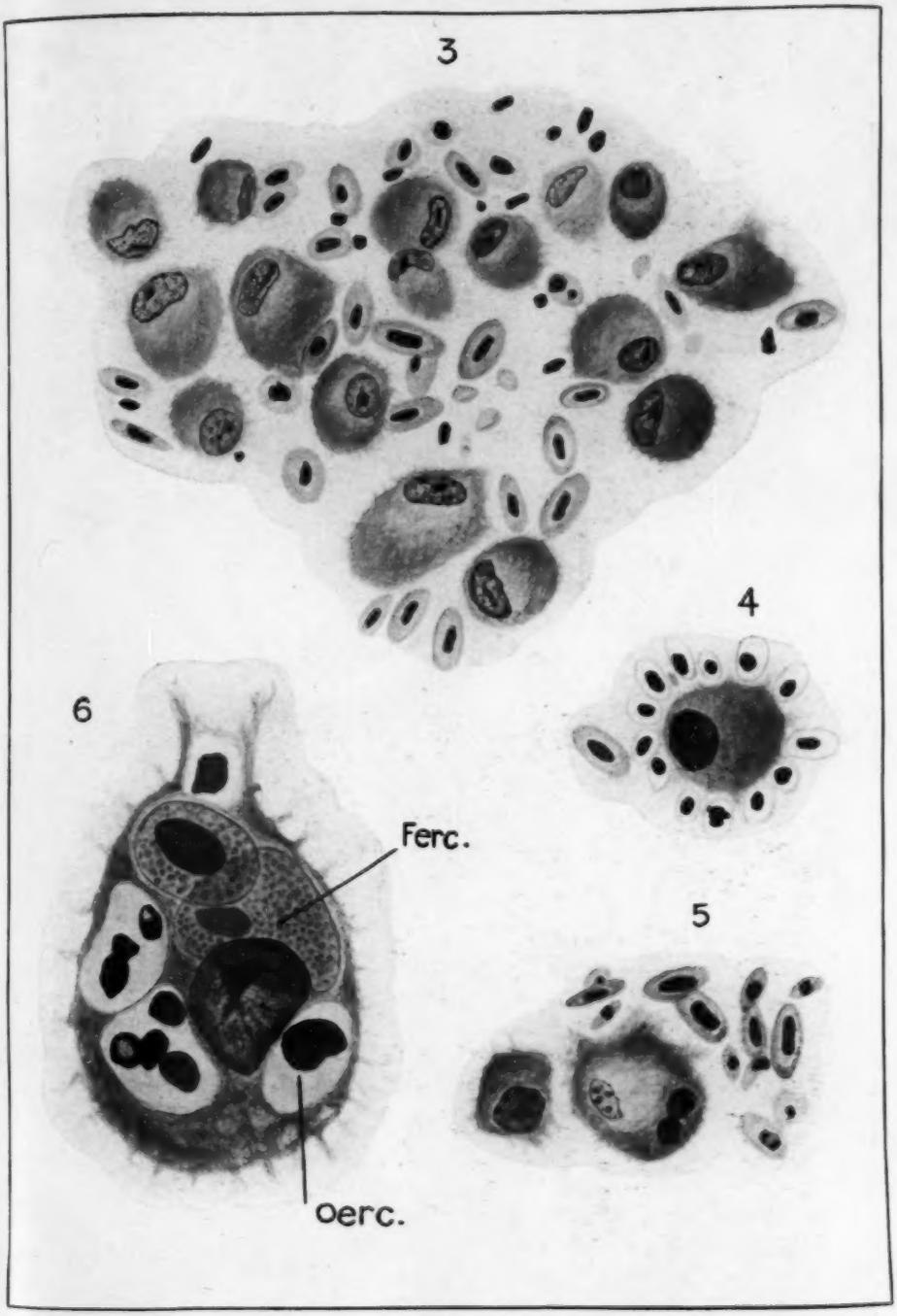
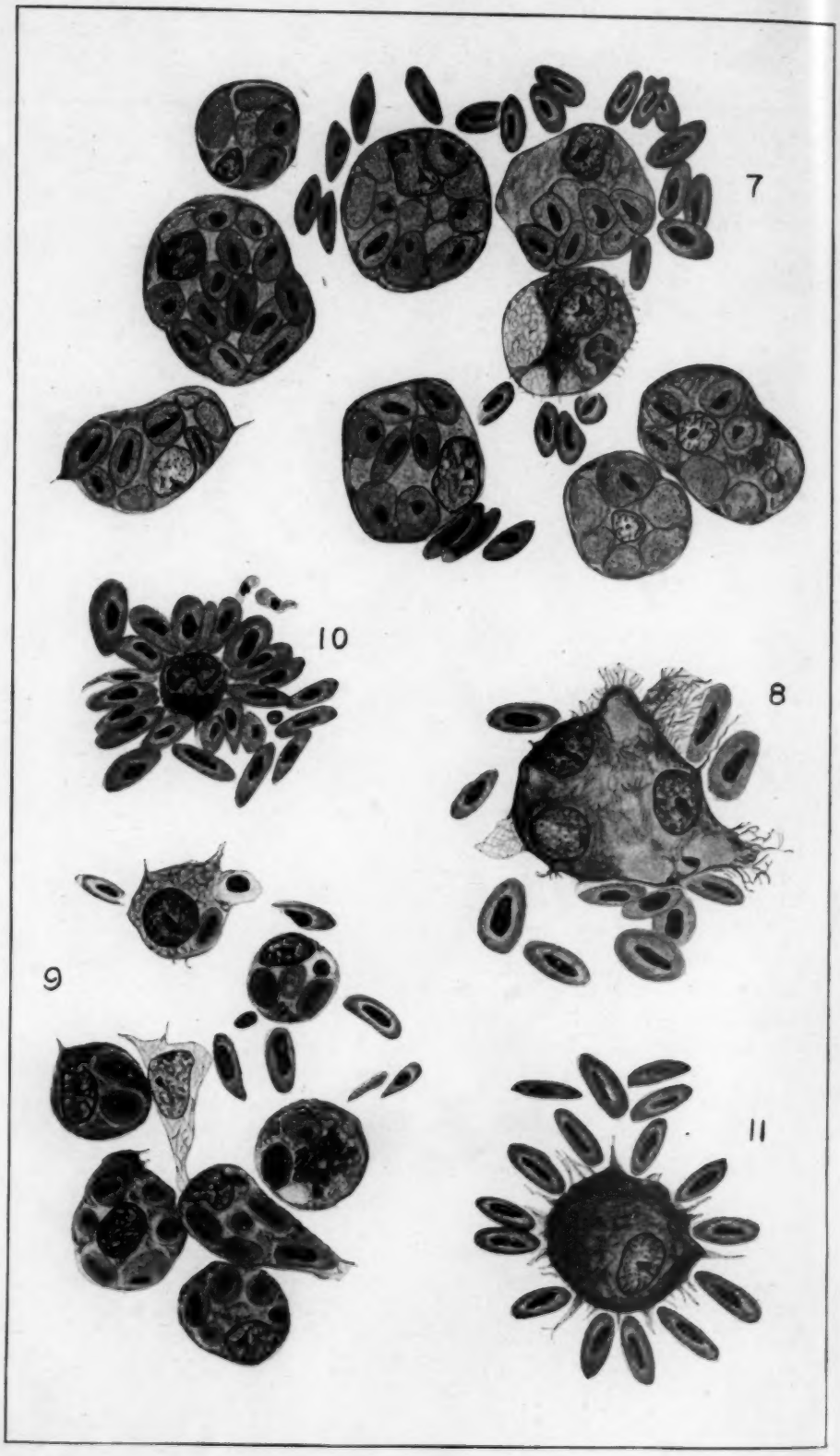


PLATE 3



The addition of immune serum to cultures from the lungs of normal rabbits in which there has not been any phagocytosis of the foreign cells produces in these cultures an extensive degree of phagocytosis. These cultures now cannot be distinguished morphologically from cultures from immunized rabbit lungs.

(*g*) *Immunologic Tests.*—The blood serum of two of the rabbits was titrated for its agglutinin content. The serum of one rabbit which received one injection of erythrocytes two weeks before explantation showed a marked agglutination of pigeon erythrocytes in a dilution of 1 to 800. The other rabbit's serum, which had received two injections of erythrocytes, showed an agglutination titer for the red cells which disappeared after the dilution of 1 to 3,000. Both of these titrations were made from serums removed from the animals shortly before they were killed for explantation.

The attempt was made to detect the presence of complement in the liquid portions of the cultures from both control and immune rabbits. These tests were made after the cultures had been living for some time, and after they had been washed with Ringer's solution at least once during transplantation. In one series of tests the fluid from the cultures in increasing dilutions, starting with 1 to 2, was incubated with known inactivated antisheep cell rabbit serum of a titration of 1 to 200 and a 1 to 30 suspension of sheep cells. Hemolysis did not result. In control tubes, to which known guinea-pig serum diluted 1 to 10 was added, complete hemolysis occurred in half an hour. Another series of tests was made in which the liquid from the cultures was used as amboceptor. Dilutions of this fluid, starting with 1 to 2, were incubated with guinea-pig serum 1 to 10 and dilute suspension of sheep cells. Hemolysis did not result in these tubes, although the control tubes with known antisheep cell amboceptor gave prompt hemolysis.

In none of my observations of the living cultures, could I obtain a definite idea as to what was taking place beneath the explant, for no matter how small a bit of tissue was, it was still too opaque to be seen through. A study of the sections of the cultures became obligatory. These were made as described above, according to the routine of Maximow's laboratory.

(*h*) *Sections of Rabbit Lung in Tissue Culture.*—In the sections the phagocytic cells show extreme variations in size. For the most part, they are roughly spherical, with numerous membrane-like pseudopodia, which vary in size and emerge from many points on the periphery of the cells. Some of these projections are so small as to be just visible—others are comparatively large, and extend for several microns in a thin, wavy, pink gray line. The phagocytes vary from 10 to 30 or 40 microns in diameter. The cytoplasm is slightly basophilic; in some cells it is markedly, in others but slightly, vacuolated. The nucleus is com-

paratively small with regard to the amount of cytoplasm; it is oval or bean shaped, and contains finely scattered chromatin dots and one or two definite nucleoli. The nuclear membrane is rather thin; it is finely wrinkled and usually shows slight irregularities and angular indentations. Opposite the nucleus the cytoplasm is decidedly acidophilic. The source of the phagocytes is easily seen in the sections. In the early stages, just as described by Lang, the septum cells are seen with their scant cytoplasm and dark resting nuclei either on or within the alveolar walls. After a few hours, the cytoplasm begins to swell and frequently becomes decidedly vacuolar. This latter appearance enables one to follow their development with ease. They soon attain a large size and are found in great numbers in and on the alveolar walls, and in the alveolar spaces. At the end of the first day's growth they have begun to wander out into the fibrin about the explant. Mitotic figures are not at all uncommon in them.

The pigeon erythrocytes vary in individual cultures in their proximity to the phagocytes. In some there are red cells close to practically every phagocyte. In others comparatively few of the phagocytes are in apposition to the red cells. In following the serial sections, as one approaches the apex of the culture, that is, away from the coverslip, the nucleated red cells frequently are found singly or in clumps in the alveolar spaces.

(*i*) *Sections of Cultures of Normal Rabbit Lungs and Erythrocytes.*—The sections show that a number of the cultures of lungs from normergic rabbits contain low grade phagocytosis of the erythrocytes by the histiocytes. This shows the importance of supplementing the study of the living cultures with sections of these same cultures, for I had no idea in studying the living cultures that the normal lungs contained as much phagocytosis as the sections demonstrated. However, this phagocytosis is still to be considered as quite low grade in that scattered cells would contain one or two erythrocytes; rarely as many as eight or nine were to be seen within a phagocyte. The cells which have phagocytized in normal lung cultures have not a constant relationship as regards their lying free in the fibrin or being in direct contact with the explant. As far as I could tell, this ability to phagocytize was independent of their neighboring phagocytic cells or the number of erythrocytes with which they were in contact. I have been unable to determine why in a group of perhaps twenty phagocytes intimately surrounded by erythrocytes, only one cell should have taken up two or three of the red cells.

An important point to be studied is the behavior of the vascular endothelium. This can be followed easily after fixation and staining. The vascular endothelium shows a marked resistance to necrosis in the center of the explant. Even after two weeks' growth in vitro the endothelium is well preserved. It is, however, quite inactive and does not show any

tendency toward proliferation, and I have not found evidence in any of the sections suggestive of the metamorphosis of endothelial cells into mononuclear phagocytes. At the edge of the explant it is not at all uncommon to find the endothelium of a capillary merging into a fibroblast-like sprout invading the fibrin.

In general the sections confirm the observations made on the living tissues to the effect that there is little or no phagocytosis of the erythrocytes by the histiocytes of the lungs of normal rabbits.

(*k*) *Sections of Immunized Rabbit Lungs and Erythrocytes.*—In the immune cultures, on the other hand, the picture is quite different. As a general rule, practically every phagocyte surrounded by erythrocytes has phagocytized. Phagocytosis here is of a much higher degree than in the normal culture, for large numbers of the histiocytes contain as many as twenty and thirty foreign erythrocytes. Here, too, the position of the phagocyte in the culture seems to bear no relationship to its ability to ingest the red cells. In those cases in immune animals in which the erythrocytes happen to lie within the alveoli they are frequently taken up by the free alveolar phagocytes, and are just as frequently, or even more so, ingested by the free phagocytes of the culture. Just as in the normergic lung cultures morphologic evidence was not found that would tend to explain the absence of phagocytosis, so here, too, it is impossible to explain why some of the scattered phagocytic cells in close approximation to foreign erythrocytes have failed to follow the example of their neighbors which are filled almost to bursting with the pigeon cells.

When the histiocytes have taken up the red cells, their appearance becomes changed from that of the normal nonphagocytizing histiocytes. The basophilic cytoplasm becomes inconspicuous except at the very edge of the cell. The latter seems distended with the large number of ingested erythrocytes which are closely packed on each other. The hemoglobin of the ingested cells may undergo two types of change; in one it becomes distinctly granular but still retains its red appearance with the eosin stain; in the other it becomes diffusely yellow green. This is caused, I believe, by the disintegration of the nucleus, so that this usually deep blue staining structure becomes a thin membrane and the basophilic nuclear substance diffuses through the orange yellow cytoplasm. The nucleus of these phagocytes becomes compressed against the edge of the cell and frequently can be made out with great difficulty.

In the sections from the immune lungs particular attention was paid to the study of the vascular endothelium. In none of the sections have I found any differences between the endothelium of the immune as compared with the normal lung cultures. The endothelium in both cases, after the addition of the erythrocytes, preserves its resting qualities. Occasionally, at the edge of the explant, it appears to be converted into fibroblasts.

(*l*) *Sections of Normal Rabbit Lung Plus Erythrocytes and Immune Serum.*—These sections show that practically every phagocyte which had been in contact with red pigeon cells had phagocytized them. The phagocytosis was even more universal in these cultures than in those from the immunized animals. The individual phagocytes at times contained many more erythrocytes than did those in the immune cultures. This was due in part to the fact that these cultures had existed for several days before the immune serum was added to them. The erythrocytes during this time became completely hemolyzed, and in this process lost in volume so that greater numbers of them could be crowded in the same space that nonhemolyzed cells would require. Those cultures which received fresh erythrocytes at the time the immune serum was added showed no apparent difference in the reaction of the phagocytes to the shadow cells and the fresh hemoglobin containing erythrocytes; both types of cells were frequently taken up by the same phagocyte with apparently equal readiness. These sections, on the whole, cannot be distinguished from those from the immune cultures; on the contrary, they can easily be differentiated from those of normal lung cultures.

(*m*) *Sections of Lymph Nodes and Erythrocytes.*—The results of my studies on lymphoid tissue will be the subject of another report. In addition to the description of the observations of the normal lymph node given previously for the living culture, it should be added here that study of these cultures when sectioned shows that the high grade phagocytosis observed in the living condition is carried on almost entirely by the large waste pigment containing histiocytes close to or still attached to the explant. These cells stand out rather sharply against the smaller nonphagocytizing histiocytes of the culture which are surrounded by large numbers of erythrocytes (fig. 2). There is, however, a complete series of transition forms between these older, pigment containing histiocytes, which phagocytize the pigeon cells, and the younger nonpigmented nonphagocytizing histiocytes. Certainly they are to be considered as members of the same cell type. When the histiocytes occurring in the lung and lymph node cultures are compared morphologic differences between the two groups can not be found.

(*n*) *Fibroblasts and Epithelium.*—We have not found any evidence of phagocytosis by fibroblasts (mesenchyme cells of Lewis and Lewis [52]) in the cultures of normal or immune lungs and normal lymph node. These occasionally grew well in the lung cultures. At times, they were difficultly differentiated from the spindle shaped cells which grew out from the bronchial epithelium. I have not seen any evidence of phagocytosis

52. Lewis, W., and Lewis, M.: Chapter on Tissue Culture, in General Cytology, Chicago, University of Chicago Press, 1924.

by the bronchial epithelium either in the original bit of tissue or in the spindle cells of bronchial origin which have migrated into the fibrin. Moreover, I have not seen any evidence of a transformation of the bronchial epithelium or the fibroblasts into the phagocytes which are so prominently present in lung cultures from the rabbit.

COMMENT

From the foregoing experiments it appears that normally in rabbit lung cultures, the added pigeon erythrocytes, although they group themselves about the phagocytes and adhere to their surfaces, are seldom phagocytized. In the cultures from immune rabbits there is an extensive phagocytosis of the pigeon cells which starts in less than an hour after the erythrocytes are added. The cells which phagocytize in the immune cultures do not require contact with the original explant to do so. The phagocytosis may be just as extensive by the histiocytes in the fibrin some distance from the explant as in those still adherent to the surface of the tissue. Difference was not noted between the reaction of the lungs from those rabbits which had received one and those which had received two injections of the pigeon cells before explantation. This observation is in agreement with the work of Gerlach and Finkeldey, who did not find any difference between those guinea-pigs which were killed in anaphylactic shock due to chicken erythrocytes, and those guinea-pigs which were killed while reacting to another injection of erythrocytes after desensitization.

A high degree of phagocytosis can be produced by adding dilute immune serum to cultures of normal lungs in which there has not been any phagocytosis. I have failed to find free complement in the various types of cultures. This, together with the facts obtained from the addition of the inactivated immune serum, indicates that phagocytosis takes place in the presence of the heat resistant immune body. I have not tested the specificity of this reaction as regards various types of blood corpuscles.

Cultures from normal lymph nodes show, beginning with eighteen hours after the addition of the foreign red cells, a gradually increasing, extreme degree of phagocytosis by the large waste pigment containing histiocytes which are usually in close contact with the explant. In the living cultures such cells with their burdens of nucleated erythrocytes were seen to glide away from the explant into the fibrin. For the most part, in cultures of lymph node, the smaller histiocytes did not phagocytize in the two days during which these experiments were continued.

On the basis of the experiments in which immune serum when added to nonphagocytizing normal lung cultures produced a high degree of phagocytosis, I would suggest that the phagocytosis which occurs in the lung cultures of immune rabbits may be due, in these cultures, to

the explantation with the tissue of small amounts of immune serum. In the perfusion experiments mentioned before, I found it impossible to cleanse completely the capillaries of erythrocytes, and it is probable that immune serum was also left in these vessels. Although I cannot speak definitely on this point, I believe that the weight of evidence to be gathered from these experiments points to the fact that the phagocytes, in the lung, are acting under the influence of the immune bodies present in the serum and that the cells, in the lung at least, have not been visibly changed while the animal was being immunized.

I have had some difficulty in explaining the inability of these lung phagocytes to take up the foreign erythrocytes. According to the view of Lang, to which I also subscribe, these cells arose from immature histiocytes, his septum cells. In the adult, normal lung these are somewhat inconspicuous resting cells which, under the stimulation of carbon particles or bacteria or explantation, can be mobilized and assume the functions of phagocytes. As Lang showed in tissue culture, they can store lithium carmine and can react to tubercle bacilli by ingesting them and can form masses of epithelioid cells against this organism. It is possible, therefore, that the phagocytes in lung cultures are not completely differentiated histiocytes and may possibly lack some of the potentialities of fully developed histiocytes found in the hemopoietic organs of adult animals. In favor of this view are, to some extent, the in vivo experiments of Briscoe, who noted that for a long time after the erythrocytes were present in the alveoli of the lungs of normal guinea-pigs little or no phagocytosis took place. He attributed the late appearing phagocytosis as being due to the appearance of increasing amounts of opsonin in the alveoli. One explanation of the failure in phagocytosis in the normergic lung cultures then could be based on the assumption that the histiocytes here are immature, but can, however, phagocytize in the presence of immune serum.

On the basis of the work of Metchnikoff and many others one could consider the serum immune bodies as being made in those organs rich in phagocytes which have experience in destroying antigen, as the spleen, bone marrow and lymph node. Therefore, the immune bodies in the blood serum could be looked on as a mobilized readily available material which enable the local immature phagocytes, such as my lung phagocytes may be, to destroy foreign proteins which gain entrance to any part of the body, be it the lungs, the subcutaneous tissue or elsewhere.

On the other hand, the phagocytes in my lung cultures might be considered as completely matured cells, in view of their reactions to carbon particles, lithium carmine and tubercle bacilli. According to this view, the lack of phagocytosis in my normal cultures might be explained as being due to the absence of normal opsonin. However, if this view is correct, I cannot see why the large phagocytes of the lymph node

should so readily take up enormous quantities of the foreign cells, unless it is assumed that opsonin is present in those organs richly supplied with mature phagocytes, which latter are absent from the lung in the body.

Of the two explanations offered for the absence of phagocytosis in the lung cultures, the immaturity of the histiocytes here, on the one hand, and the absence of an opsonic body on the other, I incline toward the latter view. The phagocytes in lung cultures are morphologically identical with those growing in lymph node cultures (Maximow [53]); they store vital dyes in tissue culture (Lang, Carleton); they react against tubercle bacilli by trying to localize them (Lang, Timofejewski and Benevolenskaya), and they phagocytize large numbers of bacteria in those cultures which are accidentally contaminated. Functionally, however, these histiocytes, together with the young, newly formed ones in the lymph node cultures, differ from the histiocytes in the hemopoietic organs in the organism, in that they do not react by phagocytosis in tissue culture to the presence of the foreign red cells as do the pigment containing more mature histiocytes of lymph nodes. I must stress again the fact that I believe both of these groups of cells to be members of the same cell type, and that all transition forms between the two groups are present in great numbers.

Since phagocytosis is usually absent from normal lung cultures, and since I did not find, in those cultures which received erythrocytes on explantation and again a week later, any evidence of phagocytosis after either addition of erythrocytes, the conclusion is probable that in tissue culture, rabbit lung does not react to the presence of an antigen by the formation of an antibody, as the experiments of Carrel and Ingebritsten and Przygode have shown does take place in cultures of spleen, lymph node and bone marrow.

A striking feature in the rabbit lung cultures is the failure of the vascular endothelium to proliferate in the monocytic or phagocytic direction. This agrees well with the observations of Maximow, who has repeatedly stressed the inactivity of vascular endothelium as a source of mononuclear wandering cells and of white blood cells as well, both in the animal organism and in tissue culture. This inactivity of the pulmonary capillary endothelium is in agreement with the observations of Schilling, Seemann, Gerlach and myself on the reaction of the endothelium of the lung capillaries in anaphylactic shock. It is at variance with the results of Oeller which were quoted in the first part of this report.

CONCLUSIONS

1. When pigeon erythrocytes are added to cultures of lungs from rabbits immunized against these cells, large numbers of the foreign corpuscles are ingested by the phagocytes of the culture.

53. Maximow, A. A.: Arch. mikr. Anat. **96**:194, 1922.

2. Phagocytosis practically does not occur when pigeon erythrocytes are added to cultures of untreated control rabbit lungs.

3. Normal rabbit lung, in culture, can be made to phagocytize pigeon erythrocytes by the addition of either untreated or inactivated immune serum to the cultures.

4. The vascular endothelium in these cultures plays a passive rôle. It takes no part in the formation of the phagocytes.

5. Differences were not noted in the reactions of the lung cultures from the rabbits which received one injection of erythrocytes and those which received two injections of the same cells.

6. The lung of the rabbit contains many mesenchymal cells (septum cells of Lang) which are but partially differentiated in the histiocytic direction. Under certain stimuli, these cells can be mobilized. They require the presence of a blood serum antibody, natural or acquired, to react in tissue culture by phagocytosis to an antigen such as pigeon erythrocytes.

EXPERIMENTAL STUDIES ON THE RETICULO-ENDOTHELIAL SYSTEM

I. RESPONSE TO INFECTION

MAX A. GOLDZIEHER, M.D.
AND
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BROOKLYN

Numerous observers have shown the important rôle of the reticulo-endothelial system in defensio. Goldzieher has emphasized that splenic swelling in infections is due mainly to a hyperplasia of the reticulo-endothelial elements. It is impossible, however, to trace the chronological course of the changes from human material alone. We have, therefore, attempted to do so by experimental methods.

Thirty mice were vitally dyed by subcutaneous injections of trypan blue, and twenty-five were left unstained. Twenty stained and twenty unstained mice were used in the actual experiments, and the remainder served as controls.

Pneumococci types 1, 2 and 3 were passed through several mice, so that their virulence was raised. A saline suspension of fresh twenty-four hour cultures of all of these was made. One half of this material was then heated at 60 C. for one hour. The animals were divided into four groups. Groups 1 and 3 each contained ten vitally dyed animals, while groups 2 and 4 contained equal numbers of unstained animals. Each of the animals in groups 1 and 2 received intraperitoneal injections of 0.5 cc. of the saline suspension containing the viable organisms, while those in groups 3 and 4 received equal amounts of the heated suspension. The animals were then killed one, two, six and twenty-four hours after inoculation.

After many staining methods had been tried, it was found best to stain the vitally dyed sections with Delafield's hematoxylin from one to three minutes, and then to wash them in tap water to which a few drops of acid had been added. This stained the nuclei a deep red, while the cytoplasm was much lighter. The trypan blue granules were well demonstrated against this background, and there was no danger of overstaining as in the other technics in which eosin or safranin were used. Even the finest granules were well demarcated.

OBSERVATIONS AFTER STAINING

The Liver.—One hour: Conspicuous changes were not seen in the Kupffer cells in any of the groups. The number of Kupffer cells, especially in the vitally dyed animals, was increased, but this was not much greater than that observed by

vital staining alone (fig. 1). Definite morphologic change did not occur in the individual cells. Some of the larger veins in sections from group 3 contained a considerable number of trypan blue cells which were interpreted as cast off Kupffer cells.

Two hours: All of the groups showed more marked changes. The increase in the number of Kupffer cells was most noticeable, however, in group 3 (stained, heated).

Six hours: All of the animals showed a further increase in the number of Kupffer cells although groups 3 and 4 showed considerably less. A study of the individual cells demonstrated that the proliferation was brought about mainly by amitotic division. Many of the intertrabecular capillaries were lined by chains

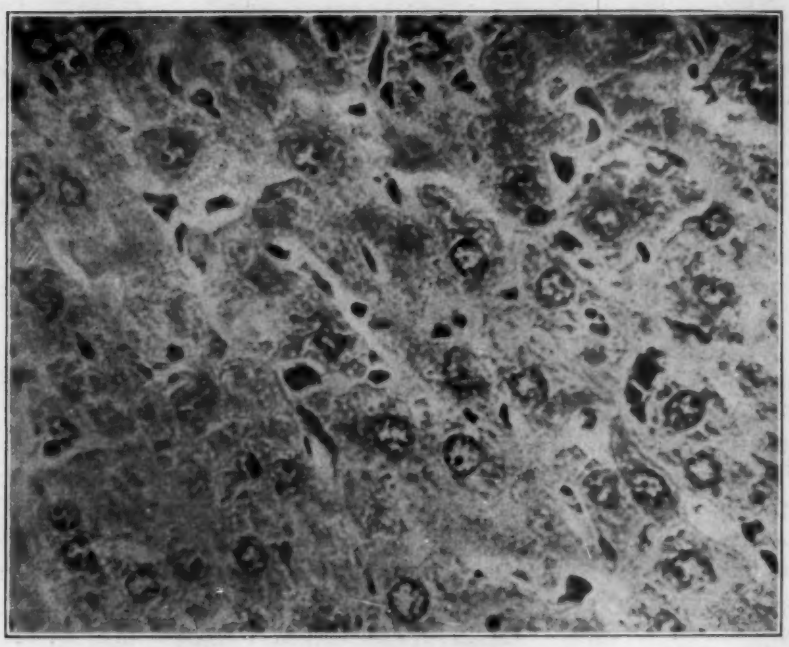

Fig. 1.—Vitally dyed liver, one hour; heated culture injected; slight increase in Kupffer cells. Leitz apochrome 4 mm., periplane eyepiece 6.

of Kupffer cells, many of which had double nuclei, but in which accompanying division of cytoplasm could not be seen. While in the normal mouse liver the Kupffer cells lie flat against the adjacent liver cells and have a spindle or thin rod shaped nucleus with a dense chromatin, the six hour sections showed an increase in the size of the nucleus, a loss of its spindle or rod shape and a swelling up to form an elongated oval. With the lessened density of the chromatin the nucleus appeared paler, approaching the vesicular endothelial type. The changes were not universal in the sections as a considerable number of Kupffer cells were seen whose nuclei did not show changes. The changes described above were encountered in all the groups but were most marked in groups 3 and 4.

Twenty-four hours: The increase in the number of the Kupffer cells in groups 1 and 2 was striking. In groups 3 and 4 the height of the reaction seems to have been reached in the previous stage, or at least morphologically there was little

difference. The changes were especially well brought out in the vitally dyed animals in which the proliferation of the reticulo-endothelial elements was demonstrated selectively. The number of trypan blue containing cells gradually increased during twenty-four hours (fig. 2). In the nondyed animals the large numbers of polymorphonuclears obscured the picture to some extent. Scattered throughout the liver were areas which showed degenerative changes in the liver cells and their nuclei. At those points proliferation of the adjacent Kupffer cells could not be seen. The degenerative changes of Kupffer cells which were occasionally encountered in the earlier stages were now quite apparent. They consisted chiefly in fragmentation of the nuclei, the pieces of which were irregularly shaped and similar to the so-called myelin figures.

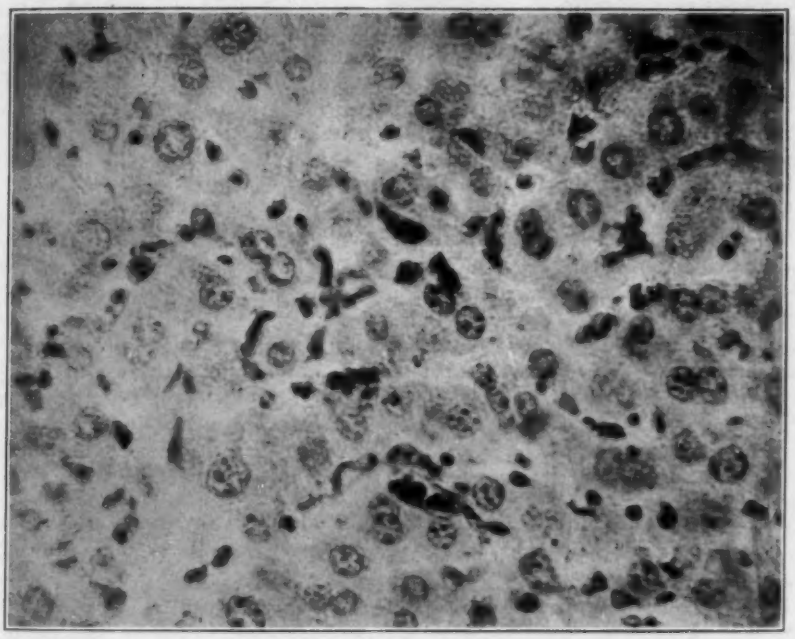

Fig. 2.—Vitally dyed liver, twenty-four hours; great increase in Kupffer cells; viable culture injected. Leitz apochrome 4 mm., periplane eyepiece 6.

The Spleen.—One hour: Just as in the liver, few changes were seen at this stage. The spleens of normal mice show comparatively much larger follicles than those in the human being with but a scanty pulp between. Giant cells form a conspicuous pulp element. They have a round cell body, with a homogenous cytoplasm, in the center of which is a large horse shoe shaped nucleus or sometimes a group of several oval nuclei. These nuclei, apparently of the endothelial type, are vesicular and contain comparatively little chromatin. The large, fully developed, giant cells do not show vital staining. In the vitally stained animal the reticulum cells of the splenic pulp were much larger than normal with an even paler nucleus than that of the unstained spleen.

Two hours: There was little difference in this stage from the previous stage.

Six hours: Low power examination showed that while the follicles them-

selves were little changed, they were now separated more widely because of the increased pulp. The vitally stained animals showed a definite increase in the number of trypan blue containing cells. The number of giant cells also was increased. Besides these there were smaller giant cells with a less abundant cytoplasm, many of which took the vital dye. A careful study of the reticulum cells showed transition forms into these smaller giant cells. They were formed partly by amitotic division and partly by fusion. Many of the large giant cells showed regressive changes. Some of their nuclei had such a reduced chromatin content that only a nuclear shadow could be seen, and some of the cells did not have any nuclei, only a round homogenous cell body which stained readily with eosin (fig. 3).

Twenty-four hours: In groups 3 and 4 (heated organisms injected) the maximum reaction seems to have been reached at six hours, but in the first two groups the changes continued and the degenerative process also increased (fig. 4). Scattered foci of degeneration could be seen throughout the pulp. Many of the reticulum cells were swollen, and the dye, instead of appearing in fine granules or lumps, now stained the cells more diffusedly.

The previous description shows that the reticulo-endothelial system responds to bacteria and their toxins by proliferative changes which could be readily demonstrated in both the liver and the spleen but which were more marked in the former. The proliferative process set in shortly after infection and gradually increased with its duration. In the experiments with bacterial toxins (groups 3 and 4), the reaction became evident sooner and reached its height in about six hours. This obviously depended on the presence of bacterial toxins, which in groups 3 and 4 were introduced directly, while in groups 1 and 2 they were the product of an active process and reached an equal and, finally a higher, concentration later. For this reason, the final reaction was quantitatively greater in the experiments with the viable organisms. Along with the proliferation of the Kupffer cells there was a desquamation, so that many vitally dyed cells were seen in the hepatic vessels. As the proliferation continued, degenerative changes were observed, and in our experiments they reached their maximum in twenty-four hours.

The most severe degenerative changes of the liver cells were found in the areas in which adjacent Kupffer cells showed the least response. This may have been due to the inadequate protection of the liver cells by the reticulo-endothelial elements at that point, or injury to the liver cells may perhaps have rendered this response impossible. At any rate, this fact seems to emphasize the close trophic relationship between the two.

In the spleen the changes in the pulp were in keeping with those of the Kupffer cells. During the course of vital staining a number of animals died, and the livers were found to be greatly infected with parasites. The animals which survived were free from infection. Apparently, vital staining interfered with the mechanism of resistance of the animals, and death resulted.

The immediate response of the reticulo-endothelial system to infection was by proliferation and, as in the human cases, the increase in the size of the spleen was due mainly to the proliferative changes.

Many experimenters have emphasized the rôle of the reticulo-endothelial system in the production of immune bodies. At first, the toxic bacterial products served as a stimulus to the reticulo-endothelial system, which was expressed morphologically by proliferation, but with the increase in toxicity many of the cells degenerated. Both proliferative and degenerative changes showed the selective affinity of the bacterial products for the reticulo-endothelial cells and were further proof of their activity in defensio.

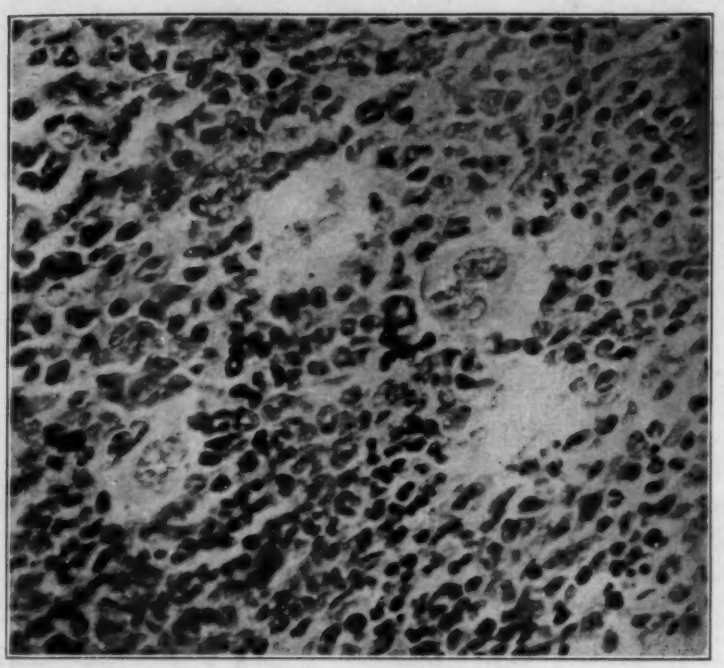

Fig. 3.—Vitally dyed spleen, six hours; viable culture injected; four giant cells in various stages of chromatolysis. Leitz apochrome 4 mm., periplane eyepiece 6.

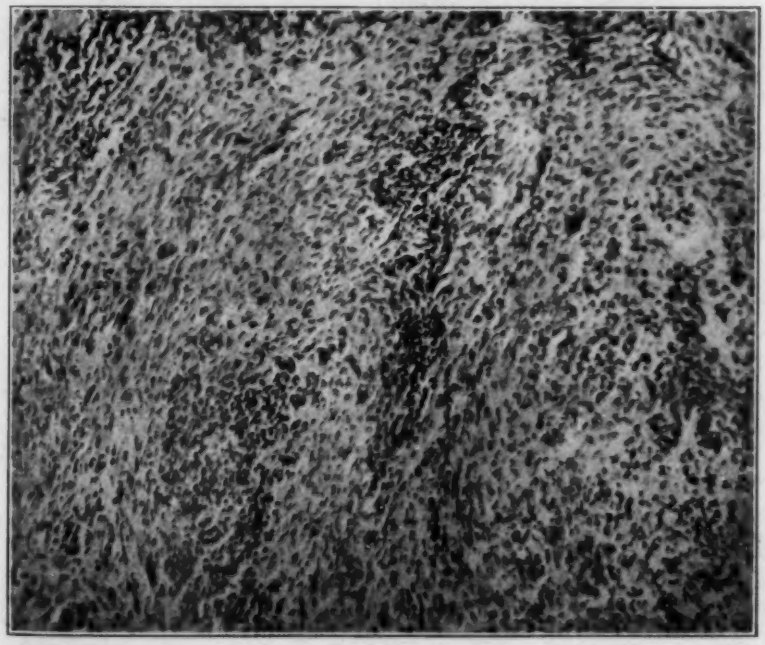

Fig. 4.—Vitally dyed spleen; hyperplasia of pulp and reticulum cells; viable culture injected. Leitz apochrome 60 mm., periplane eyepiece 6.

On weighing the spleen of dyed and nondyed animals the latter were found to be about 35 per cent lighter. When the average weights of the spleens of the various groups were compared it was seen that in groups 1 and 2 in which the active infection was present, there was a gradual increase of weight in twenty-four hours, while in groups 3 and 4 the increase was at its peak at the six hour period, and the dimensions of the two previous groups were not reached. This seemed to support our morphologic observations.

SUMMARY

The early response of the reticulo-endothelial system in experimental infection was striking. The first demonstrable changes were those of proliferation, and they increased with the progress of the infection. Degenerative changes became apparent somewhat later and also more marked with the duration of the process. The reticulo-endothelial system responded more quickly to the administration of bacterial toxins than to bacterial infection itself. The final response, however, was greater in the latter. In vitally stained animals the reticulo-endothelial cells at first responded somewhat slower, but finally the increase in response exceeded that of the unstained animals—both those in which there was active infection and those in which toxins alone were administered. The reaction of the reticulo-endothelium of the mouse was more striking in the liver than in the spleen.

EXPERIMENTAL STUDIES ON THE RETICULO-ENDOTHELIAL SYSTEM

II. EFFECT OF MERCURY SALTS AND SULPHARSPHENAMINE ON RETICULO-ENDOTHELIAL CELLS *

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Shortly after experiments in which we studied the rôle of the reticulo-endothelial system in the defense of the organism against infectious agents and their toxins,[1] we attempted to determine whether injections of various drugs, such as mercuric chloride and sulpharsphenamine, might not induce an analogous process. Mercuric chloride exerts a germicidal effect in vitro, in sufficient concentration. However, when we consider the dilution reached in human or animal organisms after therapeutic administration, it is hardly conceivable that the results obtained are due to these direct germicidal properties. Besides the extreme dilution, we must consider also the close contact of the mercury salt with the protein suspensions of the blood plasma which would certainly interfere with its effect on the parasites. Although we admit that sulpharsphenamine may have some direct germicidal effect on the spirochetes, a single injection is not the sterilizing dose that Ehrlich had hoped for.

It has been maintained that injections of mercury salts, as well as those of other heavy metals, increase the production of antibodies (Neuber,[2] Walbum,[3] Schmidt [4]). Other experimental work, which has revealed the connection between antibody production and the reticulo-endothelial system, suggests that reticulo-endothelial activities might account for the curative effect of mercuric chloride in syphilis. There are also observations (Schlossberger,[5] Del Baere [6]) which indicate a spe-

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* From the Pathologic Department, United Israel-Zion Hospital.

1. Goldzieher, M. A., and Peck, S. M.: Experimental Studies on the Reticulo-Endothelial System: I. Response to Infection, Arch. Path. **3**:629, 1927.

2. Neuber, E.: Orvosi hetil. **29**:295, 1910.

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cial affinity of the reticulo-endothelial cells for sulpharsphenamine. We therefore undertook to study histologically the response of the reticulo-endothelial system to both mercuric chloride and sulpharsphenamine.

EXPERIMENTS WITH MERCURIC CHLORIDE

A group of thirty rats was used, fifteen being vitally dyed with trypan blue and fifteen unstained. Ten animals from each group were used in the actual experiments while the remainder served as controls. Each of the twenty rats received 0.0004 Gm. of mercuric chloride

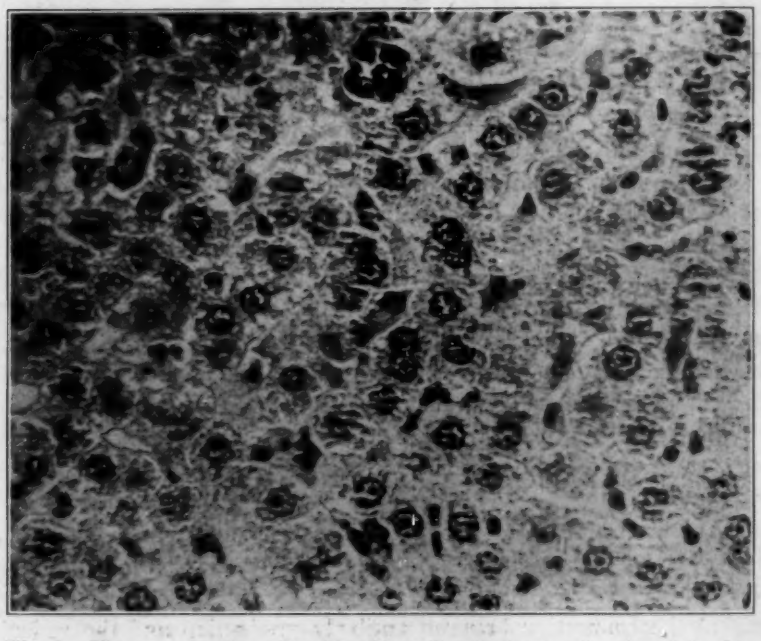

Fig. 1.—Numerous and swollen Kupffer cells, six hours after last injection of mercuric chloride. Leitz apochromatic 8 mm., periplane 6.

per hundred grams of body weight, injected subcutaneously in three doses, at five days intervals. The saturation of the reticulo-endothelial system with vital dye was maintained by injections of trypan blue, at suitable intervals during the course of the mercury treatments. Since the control animals received simultaneous injections of the dye, the effect of dye alone on the reticulo-endothelial cells was adequately controlled. The animals were killed one, three, six, twenty-four and forty-eight hours after the last injection of mercuric chloride. The livers and spleens were examined after fixation in formaldehyde, Zenker's solution and osmic acid.

Liver.—The most striking changes were found in the animals of the three and six hour groups. The number of Kupffer cells was increased and the cells themselves showed a remarkable increase in size (fig. 1). Some of them attained the proportions of large ganglion cells and resembled such cells closely because of their many dendritic processes. Many were still elongated and flat, but the amount of the cytoplasm was much greater than that of the normal Kupffer cells of the rat. The changes were more apparent in the stained animals, probably because of the better demarcation. The cytoplasm of the larger cells particularly showed a number of vacuoles, which, however, were not large, never

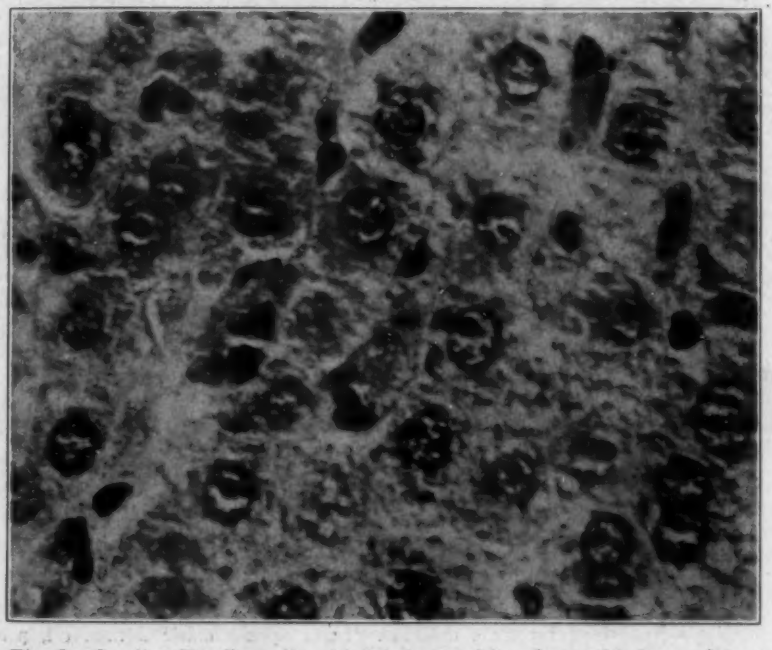

Fig. 2.—Swollen Kupffer cells with lobular nuclei—others with large elongated nuclei; cytoplasm finely vacuolated. Leitz apochromatic 4 mm., periplane 12.

reaching the size of a red blood cell. Parts of the cytoplasm seemed to be denser and cloudier than others, but the cell processes were more homogeneous. There were also certain differences in the staining properties of the cytoplasm. Some of the cells showed a greater affinity for basic stains, while others did not take them at all. The nuclei of the Kupffer cells were markedly increased in size. Many of them were from five to six times as large as the average reticulo-endothelial nucleus (fig. 2). They all showed a much less dense chromatine, and many were decidedly vesicular. While some nuclei were oval or even irregularly round, others were greatly elongated. The changes in the nuclei, how-

ever, were not uniform. A number of cells did not show any nuclear changes to speak of.

The swelling of the Kupffer cells, which apparently reached its height between three and six hours, decreased considerably after twenty-four hours, and the changes in the cytoplasm were no longer recognizable in the forty-eight hour specimen. The nuclear changes, however, were still apparent in the twenty-four hour specimen, but to a lesser degree. The number of Kupffer cells, on the other hand, had apparently increased in this latter stage and seemed to persist in the forty-eight hour specimen.

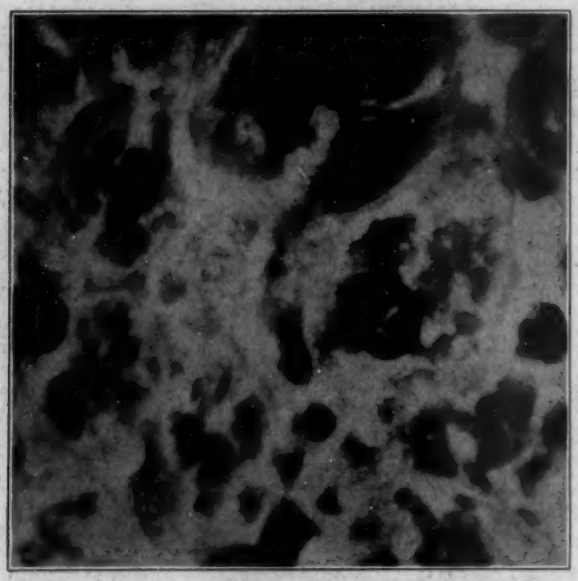

Fig. 3.—Phagocytosis of an erythrocyte by swollen Kupffer cell, six hours after last injection of mercuric chloride. Leitz apochromatic 2 mm. oil, periplane 12.

In the control animals, the trypan blue appeared in the form of lumps and fine granules in the cytoplasm of the Kupffer cells. After mercuric chloride was injected there was a much greater diffusion throughout the cytoplasm although many of the Kupffer cells still contained blue granules after three hours. The six hour group showed an almost complete disappearance of the granules, and only a fine diffuse bluish color could be seen. This also gradually disappeared, so that in the forty-eight hour groups there was hardly any difference between the stained and the unstained animals.

Another interesting observation was the increase of red cell phagocytosis in the Kupffer cells. While a phagocytosed red cell was occa-

sionally found in the normal livers, the number was visibly increased after the mercuric chloride injections. The phagocytosed red cells appeared normal in size and shape and were usually found in vacuoles of the swollen Kupffer cells (fig. 3.)

Spleen.—The early response of the spleen to mercuric chloride consisted of an increased hyperemia in the small pulp areas, around and between the follicles. As early as three hours after injection there was a swelling of the pulp reticulum cells, while the reticulo-endothelial cells of the follicles seemed to be affected at a later period. The morphologic

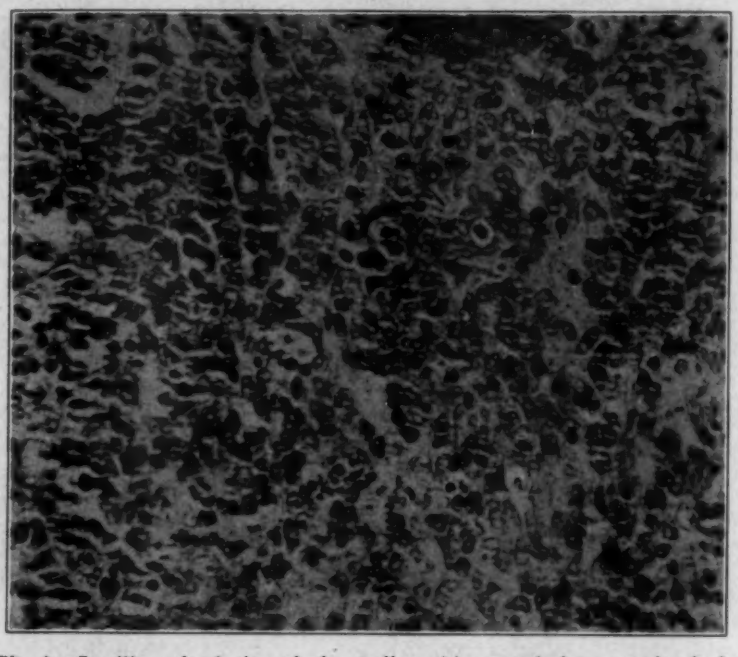

Fig. 4.—Swelling of splenic reticulum cells and increased phagocytosis, six hours after last injection of mercuric chloride. Leitz apochromatic 8 mm., periplane 6.

changes of the splenic reticulo-endothelial cells were identical with those of the Kupffer cells. One peculiarity, however, which was especially noticeable among the follicular reticulo-endothelial elements, consisted in an increased phagocytosis of cellular débris (fig. 4). This was marked in the macrophages which were scattered throughout the follicles. They had comparatively small nuclei with an abundant cytoplasm containing many phagocytosed nuclear fragments. The hyperemia and swelling of the pulp elements gradually subsided after from six to twenty-four hours, but on the whole this change was not as complete as in the liver.

The trypan blue had a tendency to be grouped in larger lumps and granules in the cytoplasm of the splenic reticulo-endothelial cells than in

the Kupffer cells, although many of the former showed a similar fine diffusion of the dye. Some of the granules were gathered together into large round or oval lumps, many of which were found to be extracellular. The trypan blue tended to assume a greenish hue even in the control animals, but after the mercury, with the progressive decrease in the dye content of the splenic cells, especially of the coarser granules, only a small amount of greenish blue or olive green dye was found in the twenty-four hour groups.

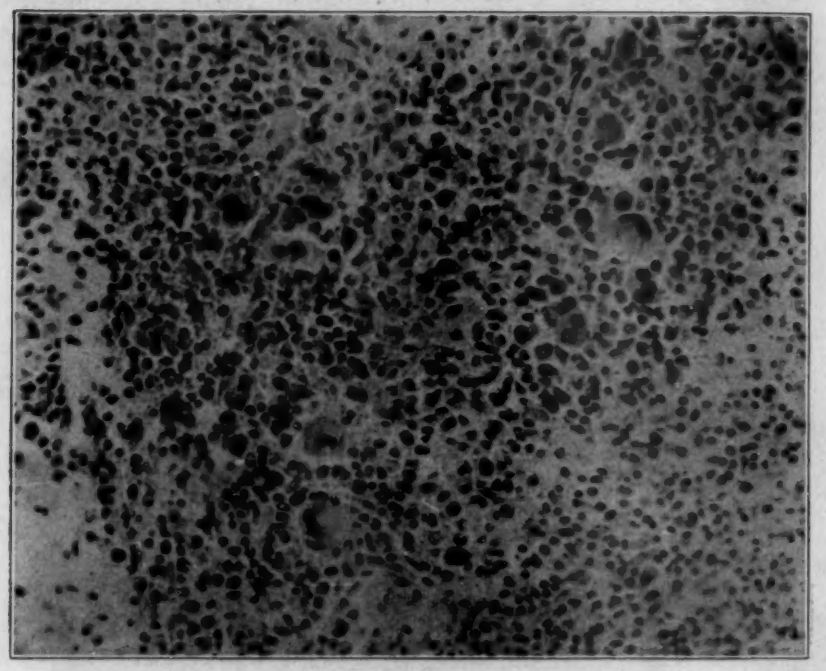

Fig. 5.—Increased number of giant cells with many plasma cells in the splenic pulp, twenty-four hours after last injection of mercuric chloride. Leitz apochromatic 8 mm., periplane 6.

The giant cells were more numerous in the twenty-four hour groups. This was especially true for the young giant cell forms (fig. 5). The formation of new giant cells was apparent at the end of six hours, but this was not true in every case.

SULPHARSPHENAMINE EXPERIMENTS

Again fifteen trypan blue and fifteen unstained rats were used. Ten stained and ten unstained animals received each 0.005 Gm. of sulpharsphenamine intramuscularly at weekly intervals for three injections. In every other respect the experiment was carried out exactly like that with mercuric chloride.

Liver.—There was little to be seen in the first hour group, but at three hours the changes were at their height. The swelling of the Kupffer cells was enormous, quite exceeding that seen in the mercuric chloride experiments. Often it was so tremendous that the swollen cells obstructed the intertrabecular capillaries (fig. 6). Most of the Kupffer cells were round and only a few retained their usual elongated forms.

Just as in the mercury experiments, the formation of vacuoles in the Kupffer cells was a prominent feature. There was, however, a marked difference in type between the two. In the mercury experi-

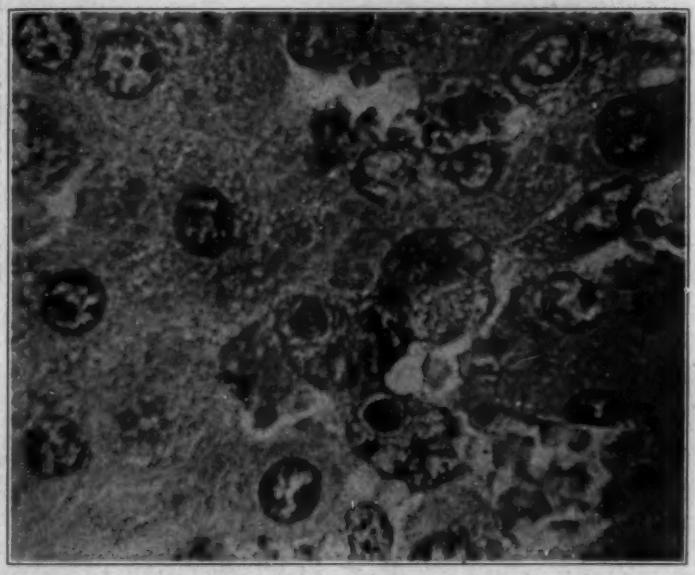

Fig. 6.—Swelling of Kupffer cells obstructing the intertrabecular capillaries, three hours after injection of sulpharsphenamine. Leitz apochromatic 4 mm., periplane 6.

ments the Kupffer cells presented a honeycomb-like structure due to the presence of great numbers of vacuoles which never exceeded the size of a red blood cell. After the administration of sulpharsphenamine usually but two vacuoles and often only one was found in each Kupffer cell, but the single vacuole was large, often exceeding the nucleus in size, and the second vacuole, when present, was much smaller.

The nuclear changes were similar to those found in the previous experiment. There was an increase in size sometimes to three or four times the original, with a lessened density of the chromatin.

There was diffuse impregnation of the Kupffer cells with trypan blue, but a good part of the dye still remained in granular form, usually surrounding the vacuoles and outlining the vacuolar wall which was distinctly blue (fig. 7).

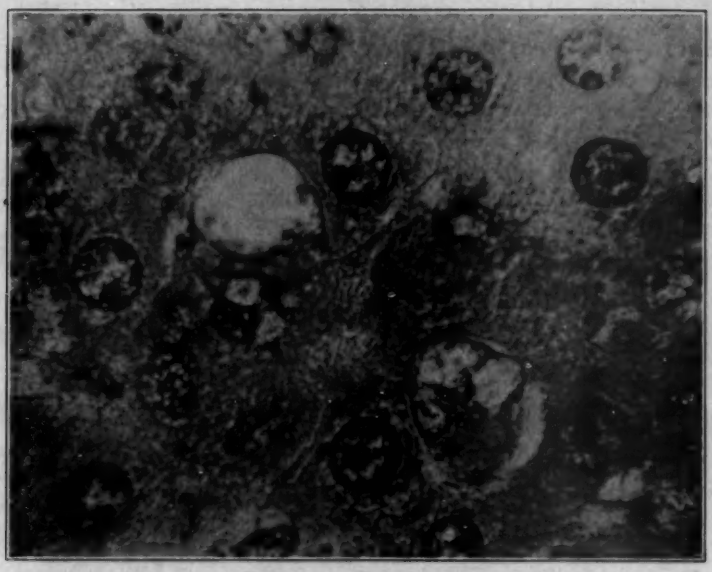

Fig. 7.—Swollen Kupffer cells with large vacuoles outlined by trypan blue granules, three hours after injection of sulpharsphenamine. Leitz apochromatic 4 mm., periplane 6.

Fig. 8.—Malphigian follicles with numerous macrophages, three hours after injection of sulpharsphenamine. Leitz apochromatic 16 mm., periplane 6.

The swelling of the Kupffer cells had gone down a good deal after six hours, but was still evident. Most of the vacuoles, however, had disappeared and in the twenty-four hour sections, the Kupffer cells appeared fairly normal, though increased in number. The disappearance of the dyestuff in the later stages was not as complete as in the mercury experiments.

Spleen.—The changes in the reticulo-endothelial elements of the spleen were more in keeping with those observed in the mercury experiments. The intrafollicular macrophages showed a much greater degree of phagocytosis (fig. 8). The changes in color of the vital dye observed in the mercury experiments were not so noticeable in these sections. There was only a slight tendency on the part of a few of the reticulo-endothelial cells to assume a greenish hue, but on the whole the color of the trypan blue was well maintained. The plasma cells were greatly increased, much more so than in the previous experiment.

COMMENT

The injection of mercuric chloride and sulpharsphenamine had a striking effect on the reticulo-endothelial cells which was equally apparent in both cytoplasm and nucleus. In the mercury experiments there was first a swelling which reached its peak in from three to six hours and then subsided, giving way to a limited amount of cellular proliferation. We believe that these morphologic changes can be explained only on the assumption of a direct stimulation of the cells. The effect on the stored trypan blue also supports this contention. The reticulo-endothelial cells after mercuric chloride stimulation apparently do not tolerate the phagocytosed trypan blue any longer. The dye stuff is dissolved and the coarser granules are expelled from the cells, and in the spleen they could be found between the pulp cells. The progressive change in color of the dye should also be attributed to an increased cellular activity.

The increased production of antibodies after the injection of metallic salts, as has been shown experimentally, is quite in accord with our morphologic observations. Both together seem to us strong evidence of the indirect action of such metallic salts against the pathogenic organisms.

The morphologic changes produced by sulpharsphenamine in the reticulo-endothelial system were even more marked and started earlier than those produced by bichloride of mercury. The Kupffer cells attained a much greater size and their tremendous vacuolization was also different from that produced by the mercury salt. There were differences too in the fate of the vitally stored trypan blue. It seemed to us, however, that the results in the two experiments were analogous in that they both represent the morphologic appearance of intense cell stimulation.

We do not believe that the vacuolization represents a degenerative process. Its quick subsidence seems to support our view. The great increase of macrophage activity seen in the Kupffer cells and splenic pulp cells in the mercuric chloride experiment, and in the follicles in the sulpharsphenamine experiment, is further proof of the increased cellular activity.

The stimulation of reticulo-endothelial activities by either mercuric chloride or sulpharsphenamine may possibly yield antibodies which circulate in the blood and body fluids and eventually may reach the spirochetes. The increased activity and particularly the phagocytic function which has been demonstrated in the spleen and liver is obviously shared by the histiocytes of the general connective tissue. For apparent technical reasons we did not try to demonstrate the morphologic response of the latter. We assume, however, that the response of the histiocytes to the drugs administered is similar to those observed in the biologically kindred splenic and hepatic reticulo-endothelial cells. Therefore, the usual antisyphilitic medication destroys the spirochetes mainly by means of reticulo-endothelial stimulation.

CONCLUSIONS

The reticulo-endothelial cells of the liver and spleen respond to mercuric chloride or sulpharsphenamine with marked swelling and vacuoli formation. These changes subside quickly and are followed by proliferation. There is also a marked increase of phagocytic activity in the Kupffer cells as well as in the reticulum cells of both the pulp and the follicles of the spleen.

In vitally stained animals the reaction of the reticulo-endothelial cells tends to eliminate the previously stored trypan blue.

All these changes were attributed to stimulation by mercuric chloride or sulpharsphenamine and may be interpreted as the expression of increased cellular activity.

It is suggested that the therapeutic effects of mercuric chloride and sulpharsphenamine are based on stimulation of reticulo-endothelial function.

RHABDOMYOMA OF THE TONGUE*

KAETHE W. DEWEY, M.D.

CHICAGO

Scarcity of records of a given pathologic condition is not always, but frequently, an index of the rarity of its occurrence. The records of rhabdomyoma of the tongue are extremely scanty; as far as I can ascertain, only seven cases have been reported. The first case is that of Weber,[1] reported in 1854, in which the tongue of a patient, aged 21, was as large as a hand, measuring 5 by 2½ inches. He called the condition "hypertrophic tongue." Microscopic features characteristic of the tumors were observed only in the new growth which developed after the first excision of the part protruding beyond the teeth. The second case, published by Pendl[2] in 1897, was that of a boy, aged 8 weeks; the growth was as large as a pigeon egg. All the other reports of rhabdomyoma of the tongue were made this year: Keynes[3] reported one case; Abrikossoff[4] three cases and Rütz[5] one case of a tumor as large as a plum in a boy, aged 5 months.

Rhabdomyomas may be divided into three groups. Those of the first group are heterotopous tumors; they occur in tissues and organs which normally have no striped muscle tissue. These growths are found chiefly in the urinogenital tract, but have also occurred in the parotid gland, the lung and elsewhere. They are mixed tumors, as a rule, and are relatively the most frequently occurring rhabdomyomas. The second group is next in frequency of occurrence and comprises tumors of involuntary striped muscle; namely, of the heart. These tumors have been well described. The third group represents the rarest type of rhabdomyoma. These tumors occur in voluntary striped muscle, such as that of the tongue and the lip, and the skeletal musculature.

In his recent report of five cases of rhabdomyoma of voluntary striated muscle, three of which were of the tongue, Abrikossoff states

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1. Weber, C. C.: Anatomische Untersuchungen einer hypertropischen Zunge nebst Bemerkungen über die Neubildung quergestreifter Muskelfasern, Virchows Arch. f. path. Anat. **7**:115, 1854.

2. Pendl, F.: Ueber ein kongenitales Rhabdomyom der Zunge, Ztschr. f. Heilk. **18**:457, 1897.

3. Keynes, G.: Rhabdomyoma of the Tongue, Brit. J. Surg. **13**:570, 1926.

4. Abrikossoff, A.: Ueber Myome, ausgehend von der quergestreiften willkürlichen Muskulatur, Virchows Arch. f. path. Anat. **260**:215, 1926.

5. Rütz, A.: Angeborenes Rhabdomyom der Zunge, Med. Klin. **22**:1072, 1926.

that up to 1918 only eight cases of such tumors had been reported and that he had not found any reports since. If these eight cases are added to those published in 1926, including my own, there are records of only sixteen cases altogether. Since eight of these were observed in the tongue alone, and only eight occurred in other parts of the voluntary musculature of the body, rhabdomyoma of the tongue must be considered as relatively the most frequent of this group of tumors.

While in the two cases of congenital rhabdomyoma and in Weber's case of "hypertrophic tongue" the tumors were proportionately large, in the other cases the growths were small, hard, slightly elevated nodules, located in the dorsum of the tongue, paler than normal muscle tissue and more or less circumscribed. In all cases the tumor was without a capsule and without evidences of malignancy. Inflammatory processes were lacking or slight. All were pure rhabdomyomas.

The microscopic appearance of such tumors is striking. The cells of which the tissue is largely composed bear no resemblance to muscle tissue; at first sight, they appear like xanthoma cells, but unlike them are not filled with fat. They are, on the whole, unusually large cells with a light protoplasm which contains numerous fine granules. These cells correspond to the embryonic myoblasts, and in some tumors no evidences of cross striation were observed; such tumors might be called, as Abrikossoff suggests, myoblastmyoma of voluntary striped muscle, or rhabdomyoma nonstriocellulare. The cells also somewhat resemble polymorphous sarcoma cells, and several writers have suggested that the "sarcomatous elements" in some rhabdomyomas, which have been mentioned in older reports, probably refer to areas within the muscle tumor occupied by myoblastic elements. The embryonic nature of the cellular elements of rhabdomyomas also accounts for the fact that rhabdomyomas appear lighter than the surrounding normal muscle tissue, for embryonic muscle tissue also is lighter than adult muscle. The characteristic histologic features observed in rhabdomyoma of the tongue are the same found in rhabdomyoma of voluntary striped muscle in other parts of the body. Cross striation of tumor cells and cell cylinders have been observed in some tumors; in other cases it was entirely lacking. Abrikossoff found cross striation in two but not in the other of his cases of tumor of the tongue; in a rhabdomyoma of the lip he observed, to a limited extent, an arrangement of the cell granules which resembled the beginning of cross striation. In Keynes' case of rhabdomyoma of the tongue, cross striation was entirely lacking.

REPORT OF CASE

History.—In the case of a woman, aged 42, a tumor, located on the anterior part of the tongue to the left of the median line, was removed in December, 1925. It appeared as a hard, grayish, slightly elevated mass measuring 1.5 cm.

in diameter. The mucosa over the tumor was not ulcerated. Slight itching or tickling, but no pain was felt. There were no palpable cervical lymph glands, and on general examination nothing abnormal was found. The swelling had been noticed first two years before, as a small elevation. There was some treatment, with no results; the growth gradually increased to the size observed at the time of the operation. The clinical diagnosis was carcinoma of the tongue (?). A *V*-shaped excision was made. The wound healed entirely, and at present, eleven months after the operation, there is no indication of a recurrence. A hurried microscopic examination of a frozen section of the tumor led to the diagnosis of fibropseudoxanthoma of the tongue. I received the specimen from Dr. I. Pilot.

The slightly elevated tumor mass was well demarcated on the outer mucosal surface as well as on the cut surface, and it measured 16 by 14 by 6 mm. It appeared denser and paler than the surrounding tissue; the papillae over the growth were slightly flattened. In a region some distance below the tumor

Fig. 1.—The tumor is well circumscribed on the mucosal and the cut surfaces, but is without a capsule. Natural size.

mass there was a relatively extensive hemorrhage in the muscle tissue which as the microscopic examination showed was not incident to the operation.

Since the tissue had been fixed in formalin examination for glycogen was not possible. A number of different stains were made: hematoxylin-eosin, phosphotungstic acid hematoxylin, van Gieson's, Mallory's anilin orange blue, Heidenhain's iron hematoxylin, Weigert's for elastic fibers with Hart's modification, and Weigert's for myelin sheaths. Sudan III and Nile blue stains and Ciaccio's, Lorrain Smith's and Fischler's methods were employed for the demonstration of fat and lipoid substances. Some of these stains require fixation in chrome salts; in those cases, secondary fixation of paraffin sections in Zenker's fluid for twenty-four hours secured entirely satisfactory staining results.

Microscopic Examination.—In all sections the tumor tissue was well defined from the neighboring tissue by the greater density of texture and the much slighter staining quality. The most striking histologic feature was the appearance of the cells of which the tumor tissue was largely composed, which at first sight resembled xanthoma cells. They were large, roundish cells with a darkly staining nucleus located in the center, and a light protoplasm which contained numerous fine granules. Although they varied considerably in size

the average diameter was greater than that of the muscle fibers surrounding the tumor mass. The average size of the cells was 38 microns; the largest measured 54 microns, the smallest 21 microns. The preexisting muscle fibers of the tissue at the bottom of the tumor showed considerable inequality of thickness; some were swollen; the largest were 42, the smallest 17 microns in diameter; the average thickness was 26 microns. The muscle fibers alongside the tumor tissue showed atrophy; their thickness ranged between 8 and 21, with an average of 14, microns.

The roundish cells, which were often polyhedral from mutual compression, extended to the epithelial border and into the papillae, and they infiltrated the

Fig. 2.—The roundish and spindle shaped light cells are distinct and separated by darkly staining, fine and thick collagenous fibers; groups of young muscle fibers intermingle with the cells; each fiber is surrounded by a space. Van Gieson's stain. Magnification 140.

adjacent muscle tissue to a slight extent. Areas in which large and smaller polyhedral cells were arranged mosaic-like alternated with areas in which the cells were joined lengthwise and formed cylinders. These were more or less parallel one to another, and were sometimes long and even and sometimes shorter, curved and interweaving, so that they appeared with tapered ends. In some of these cell cylinders the individual cell outlines were retained, in others they were more or less obscured or completely lost. The individual cells generally contained one nucleus; rarely there were two and exceptionally four

nuclei were seen together. The nuclei were as variable in size and shape as the cells. The average nucleus was roundish or oval, not large in proportion to the size of the cell and rich in chromatin, and it contained one or two large darkly staining nucleoli. Larger nuclei sometimes showed more than two nucleoli—even six could be counted; also relatively large nuclei were seen. While the larger nuclei were roundish or oval, the smaller ones were angular, cuboidal or with other irregular forms. Not rarely more or less homogeneous darkly stained small masses were seen in the cells, and particularly in the cell cylinders; they were remnants of nuclei. Throughout the entire tissue, and in all stains, the cell body with its granular protoplasm appeared light. In

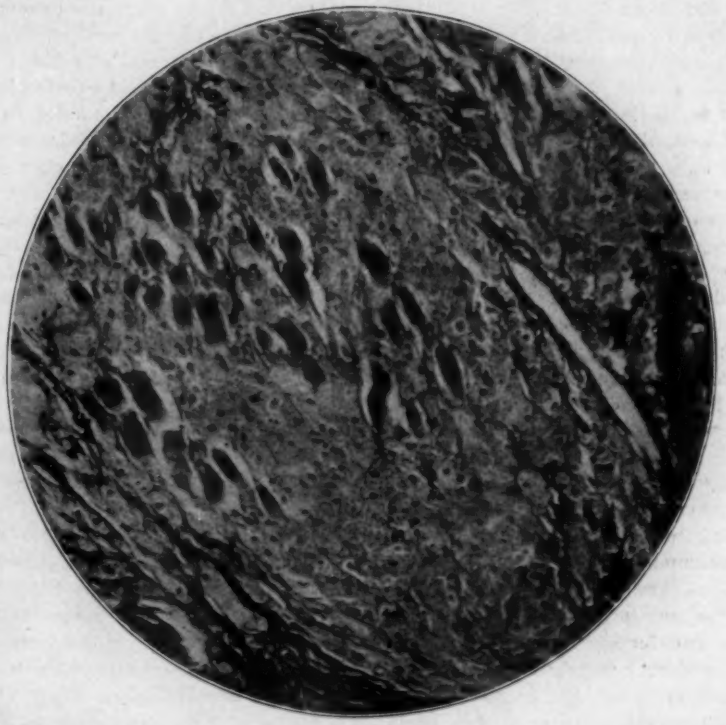

Fig. 3.—Another field in the section shown in figure 2 in which the cells are more or less completely fused and form a syncytium, while the young muscle fibers have definite outlines and are surrounded by a space. Magnification 140.

some cells the granules were close together and uniformly filled the entire cell body; in others there was the appearance of some grouping of the granules, sometimes only vague, sometimes fairly distinct. This grouping suggested an arrangement of the granules in stripes, but in no instance could it be called definite. Another grouping of cell elements, however, was sometimes observed which was definite, and in appearance absolutely identical with Cohnheim's fields. Occasionally the entire transverse surface of a cell was divided into such fields; more often only a few were seen in one cell. They were often unequal in size, and here and there a giant field of Cohnheim was seen. Such

fields were also observed occasionally on the longitudinal aspect of a cell cylinder. In this position they seemed incongruous; Cohnheim's fields indicate an arrangement of granules and a formation of fibrils in a definite direction; in adult muscle fibers they represent the cross-sections of longitudinal bundles of fibrils within the fibers. Cell cylinders are the forerunners of muscle fibers; they are formed by the union — often pell mell — of individual cells, and it was assumed that in some of the latter a grouping of granules and fibrils into bundles had already taken place, while orientation of the bundles within the cell cylinders had not yet occurred.

The cells and cell cylinders had definite outlines; but there were areas in which the cells were fused and had lost their membranes, i. e., syncytium formation had taken place. The syncytium corresponded to the plasmatic syncytium observed in embryonic life as a phase in myogenesis. The presence of delicate cell membranes, except in the syncytial masses, and of intercellular fibrils and fine and coarse fibers was well brought out by van Gieson's stain and Mallory's stain for collagenous fibers. As the cells of this tumor corresponded to the myoblasts, the intercellular collagenous fibrils and fibers represented the perimysium, including the sarcolemma. The amount of this intercellular connective tissue varied greatly; in some areas it consisted only of fine fibrils, in others it was considerable and occurred even in broad bundles which were not unlike narrow muscle fibers. The collagenous fibers were accompanied by elastic fibers. In sections stained by Hart's modification of Weigert's stain for elastin, it was found that elastic fibers were entirely absent in the syncytium and in areas in which the cells were closely packed and separated only by their cell membranes. With an increase of the intercellular collagenous tissue elastic fibers appeared. There were only a few in the cellular tissue, but they became more apparent about the cell cylinders in the neighborhood of muscle fibers about which they were always in evidence, and were present in abundance in the subepithelial tissue and the papillae where the connective tissue was more abundant. There were fewer elastic fibers about degenerated muscle fibers in the tissue outside the tumor mass.

Scattered throughout the cellular tumor tissue adult muscle fibers were found running longitudinally and transversely; they were always in groups. Some of the longitudinal fibers which were very long extended almost throughout the entire width of the tumor in the sections. There were evidences that these muscle fibers were largely, if not all, newly formed and not remnants of preexisting muscle fibers which were destroyed by the growth of the tumor. Degenerative changes were not evident in these muscle fibers, except slight ones here and there at the periphery, which were of the same type as those present in the muscle tissue outside the tumor. Here the changes were quite marked and, apparently, were not brought about by the growing tumor, but arose, perhaps, in part from disturbances due to trauma. At some distance from the inferior border of one half of the tumor there was an extensive hemorrhage, which was not of recent date, and here the muscle fibers had undergone most marked lytic alterations. Other changes of the muscle tissue around the tumor were well demonstrated by phosphotungstic acid hematoxylin, Mallory's anilin orange blue and Heidenhain's iron hematoxylin stains. With Mallory's stain the color changes of the adult muscle fibers ranged from vivid scarlet red to purplish red, lavender and purple. With Heidenhain's iron hematoxylin stain those fibers which were scarlet red with Mallory's stain were deep black. Such fibers appeared as markedly swollen, homogeneous, brittle masses in which longitudinal and cross striation had largely or totally dis-

appeared; transversely cut fibers of this kind showed clefts. In fibers showing other color reaction the original structure was also more or less obliterated. Longitudinal striation was more resistant than cross striation. All these changes were absent in the muscle fibers which occurred in the tumor tissue as a result of differentiation of the cellular elements. The process was best observed about the longitudinal muscle fibers, between and around which cell cylinders were present. Some of the cylinders already showed complete fusion of the individual cells and were as straight and evenly contoured as adult muscle fibers. In others the cell membranes were still partially or totally retained; such cylinders were twisted and unequal in width, and showed constrictions. It is to be assumed that the cells mixing with, and surrounding, transversely cut young muscle fibers were the transverse sections of cell cylinders running parallel to those muscle fibers. A grouping of cell granules

Fig. 4.—Between the young muscle fibers is a cell cylinder with contorted outlines, composed of cells, the membranes of which have disappeared in the lower part and are partially retained in the upper part; the nuclei are large and dark, and here and there a grouping of the cell granules in stripes can be seen; the two outer muscle fibers show longitudinal fibrillation and a cross striation which is fine and close, and often discontinuous; the transverse stripes of the central muscle fiber are thicker, farther apart and continuous; faint suggestion of longitudinal and cross striation in cells to the right and plainly visible Cohnheim's fields in cells to the left. Mallory's stain for collagen. Magnification 380.

that was suggestive of an initial cross striation generally was found in cell cylinders near the newly formed muscle fibers. The fact that very distinct Cohnheim's fields were seen in the cells here and there, also indicated that a systematic arrangement of elements within the cells had already taken place, but that the greater affinity for the stain was still lacking. Occasionally, however, in the vicinity of adult muscle fibers, cells were observed which were slightly darker than the other cells, which also exhibited initial stages of cross striation, while the nuclei were less distinct. The cell cylinders next to adult fibers became invested with some connective tissue like those fibers. Spaces

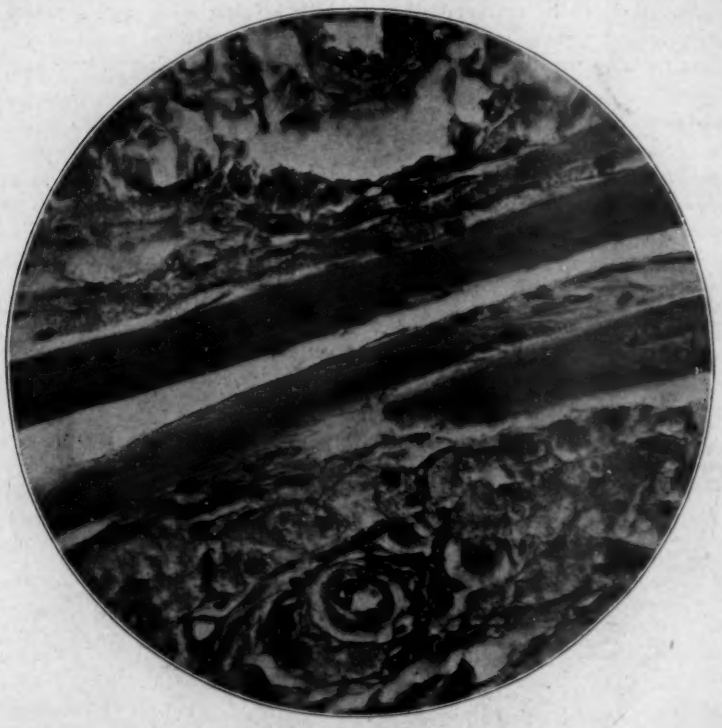

Fig. 5.—Of the three young muscle fibers in this field the upper and the lower one contain numerous large round nuclei scattered throughout the interior of the fibers; their development through fusion of many cells is obvious where shadows of cell outlines are still discernible; there is only longitudinal fibrillation in these two muscle fibers, while the more adult central muscle fiber shows distinct cross striation; there is a fairly distinct grouping of the cell granules in a longitudinal direction in the slender cell cylinder above and along the upper muscle fiber. Van Gieson's stain. Magnification 335.

which were always present about adult muscle fibers were sometimes also seen about cell cylinders adjacent to the muscle fibers. Such spaces were totally absent in the strictly cellular tissue.

An interesting feature of the developing muscle fibers was the change of the position of the nuclei. In the cells and the cell cylinders the nuclei were rather large, roundish and axial; in the adult muscle fibers they were narrower,

spindle-shaped, darker and superficial. There were also transitional fibers which already had the darker stain of young muscle fibers, but the nuclei were still roundish and scattered in the central portion of the fiber, and structurally were less distinct than the nuclei in the cells and the cell cylinders; this was due in part to the fact that they were dimmed by the darker stain of the muscle fiber. Such young fibers were sometimes as evenly contoured and straight as the more adult fibers; but the union from many irregularly shaped cells was still discernible, for shadows of cell membranes within the fibers could be seen. Apparently some nuclei perished in the course of the formation of

Fig. 6.—Tumor cells, very irregular in size and shape, occupy the papillae and are actually in contact with the epithelium; a suggestion of cross striation may be seen in some cells; the outer epithelial surface is flat and without any cornification. Van Gieson's stain. Magnification 140.

muscle fibers, for nuclear remnants were especially numerous in the cell cylinders near muscle fibers. Cross striation was less distinct in fibers with axial nuclei than in those with peripheral nuclei.

Muscle fibers obviously did not develop from one cell, nor grow by increase in length of this one cell, but they developed through the fusion of many cells. In the cell cylinders resulting from this fusion at first the nuclei were placed axially, and gradually they came to lie at the periphery. Also this process corresponded to a phase in embryonic myogenesis.

The formation of muscle fibers began at a certain distance from the epithelium. There was no indication of such processes in the tumor tissue occupying papillae and the subepithelial region. The cellular tissue in this location generally appeared lighter than the rest of the tissue.

The subepithelial tumor tissue, on the other hand, was the one in which a reaction, however slight, to the lipoid stains was observed. Abrikossoff reported of his cases that staining with scharlach R was negative. I observed a slight reaction with Sudan III while sections stained with Nile blue were negative. With Ciaccio's method which demonstrates complex mixtures of lipoid

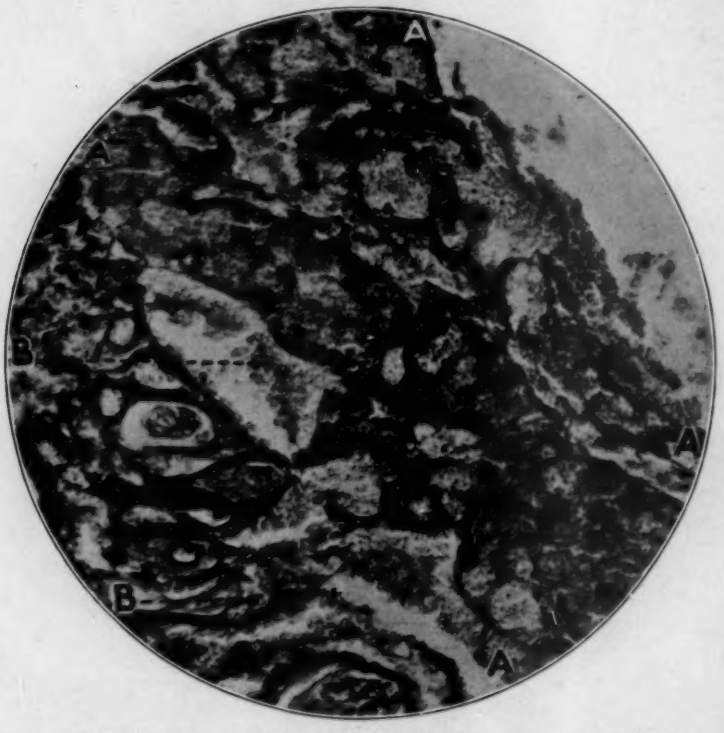

Fig. 7.—From a tongue involved in marked granulomatous infiltration with extensive destruction of the muscle tissue; in the area (*a*) to the right the degenerated muscle fibers are broken down and appear as irregular cells in which traces of longitudinal and cross striation can be seen here and there; the chief difference between these cells and those in the tumor tissue is the almost complete absence of nuclei; (*b*) blood occupying all available spaces to the left. Mallory's stain for collagen. Magnification 250.

substances, in particular kephaline, a somewhat more definite reaction was obtained than with Sudan III; with this staining, the tumor cells in the subepithelial and papillary regions appeared filled with faintly orange colored granules. Whether this reaction was more extensive than these sections indicate could not be ascertained, for the piece of tissue prepared by Ciaccio's method contained only a small area of tumor tissue. No lipoid substances

demonstrable by this method were observed in the muscle tissue outside the tumor tissue. As to Fischler's method which demonstrates fatty acids and soaps, only thick sections revealed a somewhat characteristic reaction; namely, a slaty bluish coloration of the granules in cells and cell cylinders, chiefly in the subepithelial region. Some of the muscle fibers outside the tumor tissue, however, showed a characteristic reaction to Fischler's stain, i. e., a black coloration. This was observed in the homogeneous, swollen muscle fibers staining scarlet red with Mallory's stain and black with Heidenhain's iron hematoxylin. The same reaction was observed in parts of the surface epithelium,

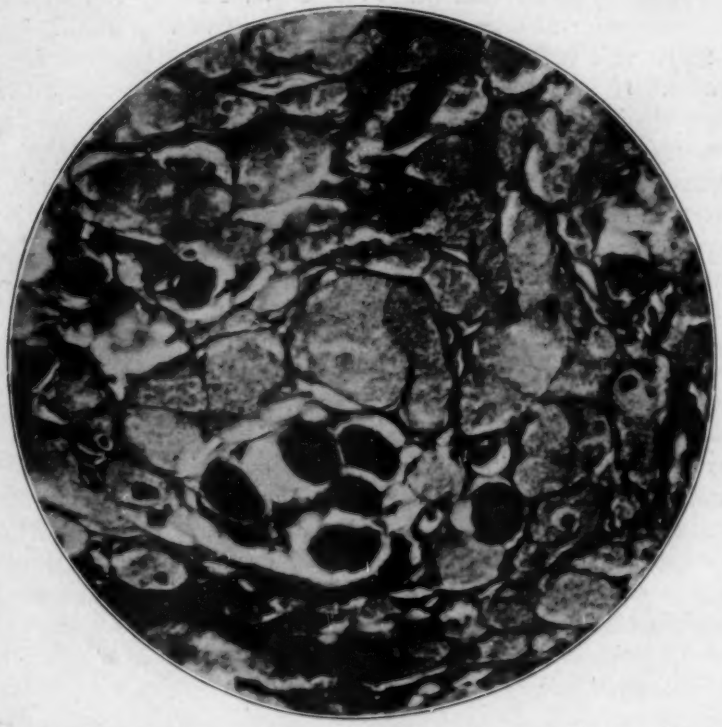

Fig. 8.—From the tumor tissue. Mallory's stain for collagen. Magnification 335.

which was cornified. From the reactions to Ciaccio's and Fischler's staining methods it might be concluded that the lipoid substances present in small amounts in some parts of the tumor tissue are chiefly of the nature of cholesterol compounds, kephaline mixtures and fatty acids. Their presence was probably an expression of degenerative changes that had taken place in these parts.

The vascular supply of the tumor tissue was limited and the infiltrative processes were slight.

COMMENT

The tumor in this case, while largely composed of atypical cells, nevertheless revealed features which clearly showed the myogenic nature of the tissue. The elements and phases of normal embryonic muscle

development were also observed, although in a more atypical manner, which is practically characteristic of tumors in general. There were deficiencies in differentiation, or abortive myogenesis. Cross striation in cells and cell cylinders was only faintly indicated by a grouping of cell granules, and a direct transition of cell cylinders with such grouping or initial cross striation into striated muscle fibers was not observed. However, there were many evidences to show that the adult striated muscle fibers found in this tumor tissue were the end-products of processes of differentiation which the cellular elements had undergone. The presence or absence of cross striation in tumors of this kind is sometimes referred to in the literature as a retention or loss of cross striation. If it is admitted that these tumors are genuine blastomas composed of embryonic tissue, cross striation at a given period has, or has not yet, taken place, but it is not retained or lost. The granular nonstriated tumor cells are at a rudimentary stage of myogenesis, and cross striation simply represents a higher degree of differentiation; i. e., it occurs later in the transformation of the granular cells into striated muscle fibers.

It has been shown by several writers that muscle tissue regenerating after destruction or injury by inflammation or tumor growth assumes appearances similar to those observed in muscle tumors. Schmincke [6] found that in all vertebrae regeneration of striped muscle is an isogenic process, i. e, it takes place from elements of the old fibers. It is either a continuous process with splitting of the fibers and budding of the ends, or a discontinuous regeneration, namely, from sarcoblasts which develop from the nuclei of the old fibers. The latter process represents cases of extremity, i. e., cases in which all the old fibers are completely destroyed and only some contractile substance with nuclei is left. In such cases the embryonic type of muscle development by sarcoblasts is resorted to. Other investigators, including Galleotti,[7] Weber,[8] Kraske,[9] Waldeyer [10] and Hoffman,[11] believe that the latter type of muscle regeneration is the

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6. Schmincke, A.: Die Regeneration der quergestreiften Muskelfasern bei den Säugetieren, Beitr. z. path. Anat. u. z. allg. Pathol. **45**:424, 1909.

7. Galleotti, G., and Levy, G.: Beitrag zur Kenntnis der Regeneration der quergestreiften Muskelfasern, Beitr. z. path. Anat. u. z. allg. Pathol. **14**:272, 1893.

8. Weber, O.: Ueber die Neubildung querstreifter Muskelfasern, in besondere die regenerative Neubildung derselben nach Verletzungen, Virchows Arch. f. path. Anat. **39**:216, 1867.

9. Kraske, P.: Experimentelle Untersuchungen ueber die Regeneration der quergestreiften Muskeln, Habilitationsschrift, Halle, 1878.

10. Waldeyer, W.: Ueber die Veränderungen der quergestreiften Muskeln bei der Entzündung und dem Typhusprozess, sowie über die Regeneration derselben nach Substanzedefekten, Virchows Arch. f. path. Anat. **34**:473, 1865.

11. Hoffman, C. E. E.: Ueber die Neubildung quergestreifter Muskelfasern, inbesondere beim Typhus abdominalis, Virchows Arch. f. path. Anat. **40**:505, 1867.

one which usually takes place, and that the old fibers perish entirely in the regeneration of muscle. According to Abrikossoff, the process may also be reversed; i. e., the preexisting striated muscle fibers lose their transverse and longitudinal striation, then become transformed into granular bands and finally break up into cells with a granular protoplasm. I observed such a breaking down of muscle fibers into cells with a granular protoplasm in a tongue involved in marked granulomatous infiltration which caused extensive destruction of the muscle fibers. Figure 7 shows an area in which the muscle fibers are broken up into granular cells which have a remarkable resemblance to the cells in the tumor presented here, but very essential elements, the nuclei, are almost entirely lacking.

As to the etiology of rhabdomyoma of voluntary striped muscle, the remains of embryonic muscle tissue may be considered, as misplaced embryonic tissue obviously is the origin of the heterotopous rhabdomyomas. There was clearly such an origin in Pendl's and Rütz's cases of congenital rhabdomyoma of the tongue. In adults such tumors of the tongue may appear to be acquired, trauma being an etiologic factor; this organ is also particularly subject to injuries of various kinds. Then, too, in these cases the condition may develop from germs of embryonic muscle tissue which was separated from its physiologic connection, or which for some reason failed to differentiate like the rest of the tissue. Trauma then is only an exciting factor that stimulates the dormant tissue to proliferate.

SUMMARY

Rhabdomyoma of the tongue appears to be relatively the most frequent of rhabdomyomas of voluntary striped muscles. It is a more or less circumscribed, but not encapsulated, benign growth.

The most characteristic microscopic feature of such tumors is large cells with a light protoplasm containing numerous fine granules, and a relatively small nucleus located in the center. These cells correspond to embryonic myoblasts.

A grouping of the granules in stripes, or initial cross striation, was observed here and there in single cells and cells of cell cylinders.

Phases of embryonic myogenesis were represented in syncytium formation, fusion of cells forming cell cylinders and various stages of differentiation in the development of young muscle fibers.

The muscle fibers in the tumor tissue are newly formed and not remnants of preexisting muscle.

There were not any evidences to prove that this growth was rather a regenerative process than a genuine neoplasm.

THE EFFECT OF LOWERING BLOOD PRESSURE ON MYOCARDITIS CAUSED BY EPINEPHRINE HYDROCHLORIDE AND CAFFEINE IN THE RABBIT*

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ST. LOUIS

The factors which cause myocarditic lesions following a single injection of epinephrine hydrochloride and caffeine have not yet been definitely determined. Fleisher and Loeb [1] suggested that excessive strain on the heart muscle may be at least one of the conditions responsible for the cardiac lesions. They refer to the typical seat of the lesion in the left ventricle near the auriculoventricular groove as favoring this interpretation. However, they did not exclude the possibility of a toxic action of epinephrine hydrochloride as a cooperative factor.

In order to test the mechanical effect of intravenous injection of epinephrine hydrochloride and caffeine in myocarditis of rabbits, amyl nitrite or sodium nitrite was administered previously, so as to counteract to some extent the blood pressure raising action of the epinephrine hydrochloride. In other cases the administration of the nitrites was combined with bleeding of the rabbit from the femoral artery, in order to lower the blood pressure still further.

I shall report first on experiments in which I wished to determine to what extent such procedures are able to counteract the blood pressure raising effect of epinephrine hydrochloride, and shall then discuss whether by the application of these methods one can modify the myocarditis caused by injection of epinephrine hydrochloride and caffeine.

EXPERIMENTS

I. *Attempts to diminish the rise in blood pressure caused by the injection of epinephrine hydrochloride and caffeine.*—In these experiments the rabbits were anesthetized by ether in each case, the changes in blood pressure being recorded by a cannula inserted in the carotid artery and connected with a revolving drum. Intravenous injections were made through the ear vein. One cubic centimeter of a mixture containing 0.2 cc. of 1:1,000 epinephrine hydrochloride and 0.25 Gm. of caffeine sodium benzoate was used for injection, in order to produce the myocardial lesion.

A. Effect of the epinephrine hydrochloride and caffeine mixture on the blood pressure: The normal blood pressure reading was 70 mm. of mercury. One cc. of the epinephrine hydrochloride and caffeine mixture was injected over a period of forty seconds. There was a latent period of fifteen seconds. The

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1. Fleisher, M. S., and Loeb, Leo: Experimental Myocarditis, Arch. Int. Med. **3**:78 (Feb.) 1909; Further Investigations in Experimental Myocarditis, ibid. **6**:427 (Oct.) 1910.

blood pressure reached the highest point (124 mm.) forty seconds after the completion of the injection. The blood pressure dropped to 54 mm. three and one-half minutes after the injection.

B. Effect of sodium nitrite alone on blood pressure: The normal blood pressure reading was 106 mm. of mercury. Two cubic centimeters of a 5 per cent solution of sodium nitrite was injected over a period of two minutes. There was a latent period of four and three-quarters minutes. The blood pressure reached the lowest point (70 mm.) in two and three-quarters minutes. The blood pressure then gradually increased up to 86 mm. in one and one-half minutes. This amount of sodium nitrite produced a methemoglobinemia; hence, smaller doses were used in the following experiments.

C. Combined action of the mixture of epinephrine hydrochloride and caffeine and of amyl nitrite: The amyl nitrite was inhaled by the animal. 1. The epinephrine hydrochloride and caffeine were followed by amyl nitrite. The normal blood pressure reading was 55 mm. of mercury. One cubic centimeter of epinephrine hydrochloride and caffeine mixture was administered. There was a latent period of five seconds. An ampule of amyl nitrite was given as the blood pressure curve began to rise. The blood pressure reached its highest point (140 mm.) in thirty-five seconds. The blood pressure fell to 55 mm. in one minute and forty seconds. 2. The inhalation of amyl nitrite was followed by the epinephrine hydrochloride and caffeine mixture. The normal blood pressure reading was 72 mm. of mercury. An ampule of amyl nitrite was given. One cubic centimeter of the epinephrine hydrochloride and caffeine mixture was injected as the blood pressure curve began to fall. The blood pressure fell to 54 mm. but then rose again to reach 144 mm. thirty-five seconds after the injection of epinephrine hydrochloride and caffeine. The blood pressure had fallen to 86 mm. one minute later.

D. In the following experiments an attempt was made to counteract the rise in blood pressure by a withdrawal of blood from the femoral artery. The bleeding was followed by injection of the epinephrine hydrochloride and caffeine mixture. The normal blood pressure reading was 115 mm. of mercury. Sixty cubic centimeters of blood was taken from the femoral artery over a period of ten minutes. At the end of this time, the blood pressure had fallen to 60 mm. of mercury. One cubic centimeter of the epinephrine hydrochloride and caffeine mixture was injected. The blood pressure reached 156 mm. in thirty seconds, and fell to 76 mm., one minute later.

From the foregoing experiments I conclude that the increase in blood pressure, which follows the injection of epinephrine hydrochloride cannot be prevented, but that its duration can be cut approximately in half by the use of amyl nitrite and also by bleeding the animal before the injection of epinephrine hydrochloride. Sodium nitrite was used in the following experiments, as well, but it proved to be of little value, inasmuch as it acts slowly over a long period of time, while the epinephrine hydrochloride and caffeine effects are marked but extend only over a short period of time.

II. *Does the lowering of the blood pressure by means of amyl nitrite, sodium nitrite and bleeding influence the myocardial lesions produced by injection of epinephrine hydrochloride and caffeine sodium benzoate?*—A. Blood pressure was first reduced by bleeding the animal. After the rabbit was anesthetized and the blood was withdrawn from the femoral artery, the epinephrine hydrochloride and caffeine mixture was injected; this was followed immediately by the administration of amyl nitrite.

Of ten rabbits treated in this way, four died soon after the injection of epinephrine hydrochloride and caffeine; of the remaining six animals, at the

time of examination, six or seven days after injection, one showed a marked lesion within the heart, two showed a slight lesion and three were without lesions. Two controls which received epinephrine hydrochloride and caffeine alone, and which withstood this injection, showed a slight lesion.

B. Blood pressure was reduced by the intravenous injection of sodium nitrite (5 per cent solution) and inhalation of amyl nitrite. The sodium nitrite was given first and followed from three to four minutes later by the injection of epinephrine hydrochloride and caffeine mixture, and immediately afterward amyl nitrite was administered.

The results in this experiment are as follows: Sodium nitrite and amyl nitrite were administered previous to the injection of epinephrine hydrochloride and caffeine to twenty-three rabbits. Of these, four died soon after the injection. Of the remaining nineteen animals, at the time of examination six or seven days after injection, six showed a marked lesion, six a slight lesion and seven were without lesions in the myocardium. Of eighteen animals which received each an injection of epinephrine hydrochloride and caffeine alone and which served as controls, two died soon after the injection, eight showed a marked lesion, eight showed a slight lesion and none was without lesions.

SUMMARY AND CONCLUSIONS

Two methods, namely, (1) blood letting combined with inhalation of amyl nitrite, and (2) injection of sodium nitrite followed by inhalation of amyl nitrite, were used in an attempt to diminish the increase in blood pressure which results from the intravenous injection of epinephrine hydrochloride and caffeine. While it was not possible by either of these methods to prevent the increase in blood pressure, both greatly hastened the return of the blood pressure to normal.

As far as the myocarditic lesions are concerned the following results were obtained: Eighteen of the control animals lived as long as six or seven days after the injection of epinephrine hydrochloride and caffeine, and all of these showed the characteristic lesion in the wall of the left ventricle. Twenty-five animals, in which an attempt was made to prevent the increase of blood pressure, lived as long as six or seven days after the experiment, and only fifteen (60 per cent) of these showed the lesion in the wall of the left ventricle. It does not seem probable that the difference in the results obtained in both series is within the range of experimental error. It appears then that the diminution in the duration of the epinephrine hydrochloride-caffeine action accomplished by the measures used prevented in 40 per cent of the animals the myocarditic changes which otherwise would have occurred. Perhaps it would be possible to prevent these changes entirely if a method could be found which fully counteracted the blood pressure raising action of injection of epinephrine hydrochloride and caffeine. One could therefore conclude that in all probability the mechanical results effected in the vascular system through the injection of epinephrine hydrochloride and caffeine and the subsequent rise in blood pressure are essential factors in the production of the myocarditic lesions following such an injection.

Laboratory and Technical Notes

HISTOLOGIC DEMONSTRATION OF THE PHOSPHATIDES AND CEREBROSIDES

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According to the various textbooks on histologic technic the fatty substances can be demonstrated by certain staining processes. The fatty substances include: (1) neutral fats; (2) cholesterol and its esters, and (3) phosphatides and cerebrosides. The first, the glycerol esters of the fatty acids, can be eliminated from this discussion for they are, as is well-known, readily demonstrable by the ordinary fat stains, especially sudan III and scharlach R. There remain, then, cholesterol and its esters and the phosphatides and cerebrosides. These are commonly included under the term "lipoids," which was introduced by Overton in 1901. The term is much abused because some authors use it to mean merely cholesterol and its esters, some use it in reference only to phosphatides and cerebrosides, while still others use it to include both these classes of fatty substances. The chemists have taken cognizance of this confusion and have introduced the term "lipin" to signify merely the phosphatides and cerebrosides. Whatever term is adopted by a given author, it should be made clear just exactly what such term stands for. In this paper the confusion will be avoided by using the chemical names.

Concerning the constitution of these fatty substances, it may be of value to point out the following. Cholesterol is a hydro-aromatic alcohol. Some uncertainty as to its exact structure still remains. It occurs frequently in the form of esters of the higher fatty acids. The phosphatides and cerebrosides are also fatty, yielding fatty acids, or their derivatives, on hydrolysis. They contain in their molecules either nitrogen or both nitrogen and phosphorus.

The phosphatides are made up of three main groups: the lecithins, the cephalins and the sphingomyelins. The first two contain two fatty acids, one saturated and the other unsaturated, combined with glycerol whose remaining hydroxy group forms an ester with phosphoric acid, and to which acid is attached an oxybase, choline in the case of the lecithins, or amino-ethyl alcohol in the case of the cephalins.

The sphingomyelins do not contain glycerol. They are constituted of phosphoric acid to which are attached the two oxybases, choline and sphingosine. To the amino group of sphingosine a fatty acid is attached.

The cerebrosides do not contain either phosphoric acid or glycerol. They are made up of a sphingosine-fatty acid combination which is attached to the reducing sugar, galactose.

According to the accepted ideas on the subject as presented by such authorities as Schmorl, Lee and Herxheimer, the staining properties of the phosphatides and cerebrosides are as follows:

1. They are not demonstrable by the ordinary fat stains such as sudan III and scharlach R.

2. Some of the phosphatides and cerebrosides appear doubly refractile. Heating does not cause this double refraction to disappear.

3. The phosphatides and cerebrosides which contain unsaturated fatty acids are blackened by osmic acid.

4. By the method of Christeller,[1] lecithin is stained.

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1. Christeller, E.: Uber eine mikrochemische Reaktion zum histologisch-färbereschen Nachweis der Fettsubstanzen, Centralbl. f. allg. Path. u. path. Anat. **27**:385, 1916.

5. Some of the phosphatides and cerebrosides are believed to be stainable by Nile blue sulphate.

However, to all these methods there is obvious objection, as far as the phosphatides and cerebrosides are concerned. Since either the neutral fats or the cholesterol fats are also stained by these methods, it would be difficult in any given section to determine the nature of the stained material. There have consequently been developed two procedures which have been accepted as demonstrating most of the phosphatides and cerebrosides: that of Smith-Dietrich and that of Ciaccio-Bell.

In brief, both these methods utilize the process of mordanting by bichromate which oxidizes the fatty substances, thereby changing their solubility and stainability. By the method of Smith-Dietrich some of the fatty substances take the Weigert stain in frozen sections. According to the Ciaccio-Bell method, some of the fatty substances are altered so that they become insoluble in paraffin, xylol and the alcohols. Paraffin sections are then stained by sudan III and scharlach R.

Extensive work has been done to show that these two methods actually stain phosphatides and cerebrosides. Chief among these are the experiments of Kawamura.[2] By first impregnating cigaret paper with the various fatty substances, and then fixing and staining according to the respective method being studied, he showed that the fatty substances which he used, including phosphatides and cerebrosides, could thereby be stained.

There are serious objections to Kawamura's work. It will suffice to reiterate what has been pointed out already;[3] namely, that both the chemical and physical properties of the fatty substances as he used them, in the free state, differ widely from those of the same substances as they exist in the tissues. Moreover, according to the chemists, the phosphatides and cerebrosides which Kawamura used were of questionable purity and in all probability contained some decomposition products, especially fatty acid compounds, the staining properties of which would vitiate the results he obtained.

By application of certain chemical properties of the phosphatides and cerebrosides, the attempt has been made to study the question of whether these fatty substances are stained by the methods mentioned above. The property referred to is that discovered by Zuelzer[4] in 1899; namely, that the phosphatides and cerebrosides are insoluble in acetone, by which substance the other fatty substances are at the same time dissolved. This is the means utilized in the chemical isolation of the phosphatides and cerebrosides.

Acetone was ideal for my purposes, for it served not only as the differentiating medium but also as a fixative.

METHOD AND RESULTS

In the histologic work the following fresh tissues were used: suprarenal, kidney, ovary, liver and heart. Blocks from 2 to 3 mm. thick were cut from each tissue and treated according to each of the following methods: (1) frozen sections—sudan III, scharlach R, Nile blue, Smith-Dietrich, Christeller and polarizing microscope; (2) paraffin sections—Ciaccio-Bell and osmic acid.

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2. Kawamura, R.: Die Cholesterinesterverfettung, Jena, Gustav Fischer, 1911.

3. Thaysen, T. E.: Einige kritisch Bemerkungen zur histo-chemischer Grundlage der Cholesterinsteatose, Centralbl. f. allg. Pathol. u. path. Anat. **26**:433, 1915.

4. Zuelzer, G.: Ueber Darstellung von Lecithin und anderen Myelinsubstanzen aus Gehirn-und Eigelbextracten, Ztschr. f. physiol. Chem. **27**:255, 1899.

Simultaneously, in each instance, an adjacent block was first extracted with acetone and then subjected to treatment identical to that of its mate which was not extracted with acetone. The results obtained with the osmic acid and Christeller preparations were not sufficiently conclusive; these methods are, therefore, excluded.

Although repeated efforts were made, all the methods failed to demonstrate any staining of the phosphatides and cerebrosides following extraction with acetone. The control tissues, which were not subjected to acetone extraction, in each case showed positive staining. It is worthy of mention also that the great amount of shrinkage which is said to occur after acetone extraction was not observed.

To prove that phosphatides and cerebrosides were actually present, a chemical determination was made of about fifty fresh ox-suprarenals. The method of estimation of alcohol-ether extraction and then precipitation by acetone, according to MacLean[5] was used; from 14 to 17 per cent phosphatides and cerebrosides were found.

My results are represented in the table.

Results Obtained in the Demonstration of Fatty Substances

	Sudan III	Scharlach R	Nile Blue Sulphate	Ciaccio-Bell	Smith-Dietrich
Neutral fats	+	+	+	—	—
Cholesterol esters	+	+	+	+	+
Phosphatides and cerebrosides	—	—	—	—	—

COMMENT

A number of morphologic studies have been made on the fatty substances in tissues under various conditions. The methods of demonstration have been those described above. It is unnecessary to discuss any individual publications of this nature, for, in the light of what has been found—namely, that the phosphatides and cerebrosides are not demonstrable by the accepted fat stains, sudan III, scharlach R, Nile blue sulphate or the special mordanting methods of Smith-Dietrich or Ciaccio-Bell—acceptance of all such work must be postponed until a positive means is found for the demonstration of the phosphatides and cerebrosides in tissues. These fatty substances occur in practically all cells of the body and are particularly abundant in certain vital tissues such as the interrenal and the brain. In what forms they exist, and what their functional significance is, must yet be demonstrated. Their appearance in increased amounts, especially in the spleen, bone marrow and lymph nodes simultaneously with certain large polygonal (Gaucher) cells, constitutes a morphologic accompaniment observed in Gaucher's disease. Similar pictures have been observed following long-standing lipemia. It is noteworthy that in the description of such material, although the authors suspected from chemical analyses of the spleen that these large cells contained phosphatides and cerebrosides, they failed to demonstrate them histologically.[6] The reason is obvious from my work.

5. MacLean, H.: Lecithin and Allied Substances, London, Longmans, Green & Co., 1918.

6. Epstien, E.: Beitrag zur Chemie der Gaucherischen Krankheit, Biochem. Ztschr. **145**:398, 1924. Lieb, H.: Cerebrosidspeicherung bei Splenomegalie, Typus Gaucher, Ztschr. f. physiol. Chem. **140**:305, 1924. Cushing, E. H., and Stout, A. P.: Gaucher's Disease, Arch. Surg. **12**:539 (Feb.) 1926.

It is an old and well-known conception that the phosphatides and cerebrosides do not exist in the tissues in the same state as the other fatty substances which are stainable. It is believed that they are in some way combined with the protoplasm of the cells. Possibly the mitochondria (whatever their significance may be) are of phosphatide nature. There are several hypotheses which tend toward this view. If the mitochondria could be demonstrated after acetone extraction, an important contribution would be made toward proving not only their chemical nature but also the significance of the phosphatides and cerebrosides in tissues.

CONCLUSIONS

1. The phosphatides and cerebrosides do not stain by the methods of Ciaccio-Bell and Smith-Dietrich. These methods, therefore, are not specific for the phosphatides and cerebrosides, as has been accepted generally.

2. Cigaret paper impregnation methods (Kawamura) are unsatisfactory for the demonstration of staining in tissues.

3. Initial acetone extraction may be utilized as the basis for the histologic demonstration of the phosphatides and cerebrosides.

General Review

DYSENTERY

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Diseases of the intestines are mentioned in the oldest document of medical nature yet discovered. From the large number of prescriptions for constipation, hemorrhoids and smarting pains of the anus and rectum in Brugsch's and Eber's papyri, one may reasonably infer that prescriptions for diarrhea and tropical dysentery were probably contained in the pages lost by mutilation. Of the religious books, the Babylonian Talmud contains clear references to dysentery which appears to have been, in part, of the chronic variety. It is noted that fever was sometimes present. In the Bible, there are occasional suggestions of the presence of this disease including a fairly good one in II Chronicles, (21-14). Jehoram, the King of the Israelites, for his waywardness was inflicted with a disease of the bowels in which these organs "fell out." The duration is given as two years. The House of David at this time had joined the House of Ahab and adopted to a certain extent the laxity of behavior of the latter. The Biblical account appears to point the lesson that had the laws of the Israelites been obeyed, such disaster would not have occurred. Preuss is inclined to consider this case carcinoma. It would be difficult to decide between the two diagnoses.

In classic antiquity, the alvine fluxes were well known and, to a considerable extent, they were classified on a clinical basis. Hippocrates used the terms diarrhea and dysentery, differentiated the two and appeared to be aware that one disease leads to another in the individual case, as also of the fact that both increase in prevalence during the same periods. The condition known as lientery (characterized by stools containing undigested food) was separated from the other two varieties. Hippocrates recognized the ages and conditions in which mortality was greater and that cases in which fleshlike material was passed were serious, also that fever and its concomitant symptoms indicated a more severe attack. Full accounts appear in the works of Aretaeus and Galen. In the "Definitiones Medicae" attributed to Galen the following definition occurs: "Diarrhea copiosior fluxio est alvi diuturna sine phlegmone et ulceratione"—indicating that a considerable knowledge of the lesions accompanying the clinical varieties had been reached at this time. The next thousand or more years do not show any evidence that this knowledge was retained or at least that it was generally con-

sidered, nor was the clear reasoning of Hippocrates, his contemporaries and his successors duplicated or approached until the eighteenth and nineteenth centuries.

During the Byzantine period, Alexander Trallianus described early epidemics but did not record pathologic observations, if such were made. During the Arabian period, the dysenteries were classified as to clinical manifestations by Avicenna, largely from the standpoint of their supposed causes. He mentions flux of blood with and without ulceration of the intestine, and ulceration without blood. As would be expected from the knowledge of this period, the ulceration was regarded as the cause rather than the result of the disease. While it is evident that postmortem examinations were made during the entire period up to the time of Avicenna, the first definite descriptions were recorded in 1506 by Benivieni. One of his cases suggests a prolonged or so-called chronic bacillary, and another an amebic infection, although from the descriptions it would be impossible to more than suggest the probable diseases present. During the sixteenth and seventh centuries, advance in the knowledge of these diseases is not particularly observed. From the pathologic standpoint, the most noteworthy feature appears to be the confusion of peritoneal inflammation with that of the lining of the digestive tract.

The treatment of the dysenteries has never been entirely satisfactory. Ipecac was first mentioned in Purchas' Pilgrimes in 1625, but it probably had been used or at least known in some areas before this time. Introduced into Paris in 1672, it was used as a secret remedy by Helvetius in 1680 and was financially backed by King Louis XIV. The first reference to emetine is by Bardsley in "Hospital Facts and Observations," London, 1830. In 1876, Woodhull, of the United States Army, published his studies on ipecac, but he was not successful in having the drug used in the treatment of dysentery to the extent to which he felt that it was justified. Vedder, in 1911, demonstrated the amebicidal properties of emetine, and in the succeeding three years Leonard Rogers standardized its use in amebic dysentery.

The semeiology of the epidemics of 1669-1672 was discussed at length by Sydenham, who said little concerning the pathologic anatomy of the condition, although it is evident that he realized the existence of ulceration in some cases. The influence of the Arabian school is plainly sensed in his writings.

In 1681, Leeuwenhoek, with the microscope of his invention, found in his own stool the organism now known as *Giardia,* the first organism described in intestinal disorder in man, the identity of which is reasonably sure.

Sir John Pringle (1752), in his capacity as Surgeon General to the British Army (1742-1758), correlated the different forms of dysentery

and recorded the result of his observation of clinical cases and autopsies. Broussais credits to John Hunter, who was Surgeon General from 1791 to 1793, the differentiation between peritonitis and inflammation of the intestinal mucosa, although it is apparent that Pringle also was aware of the distinction both clinically and anatomically. In the last decade of the eighteenth century, Matthew Baillie, the London pathologist, described the ulcerative and nonulcerative varieties of dysentery as observed at autopsy. Broussais, who rather dominated the medical thought of his period, with the idea that gastro-enteritis is "the basis of all pathology," differentiated from the anatomic standpoint, the clinical symptoms accompanying inflammation of the digestive tract (1829), and reviewed a considerable part of the available literature.

Rudolf Virchow, in 1853, discussed catarrhal and diphtheritic dysentery as stages in one and the same disease, stating that the entire colon is not always equally involved. His description of an acute bacillary case from the beginning to the autopsy is an excellent portrayal.

In 1857, Malmsten discovered the protozoan *Balantidium coli,* the largest protozoan now known to produce the clinical syndrome of dysentery. He described two cases of chronic dysentery in which this organism was present in considerable numbers. In one, ulcerations in the rectum were seen and treated locally with resulting improvement; the second patient died and at autopsy lesions typical of this condition were seen. The organisms were abundant in the cecum, where lesions were not found; ulcerations extended throughout the greater part of the large intestine, becoming larger in the sigmoid, while in the rectum there was a diphtheritic inflammation, possibly due in part to the treatment. In 1857, Lambl described *Giardia* in the intestinal secretion but did not make any comment with reference to pathologic changes. In the same year, A. Normand described a strongyloid which he found in several cases of Cochin-China diarrhea.

In 1875, Lösch discovered the ameba of dysentery in man in the bowel discharges and the scrapings of the ulcers in cases of amebic dysentery. His descriptions are typical, though he did not record the presence of the organisms in microscopic sections. He inoculated four dogs by mouth and by rectum, and in one produced a dysenteric condition which showed amebae in the dejecta and reddening with superficial ulceration of the rectum. This was the dawn of the era of parasitology, which has dominated the thought of medical men in regard to all diseases up to the present.

The greatest treatise on the subject of the alvine fluxes was written by Joseph Janvier Woodward in the second Medical Volume of the Medical and Surgical History of the War of the Rebellion, 1879, comprising 850 pages, and includes an excellent analysis of the literature up to his time. The disease is described in all its variations, each type

being beautifully illustrated from the standpoint of both gross and microscopic anatomy. Woodward was not convinced of the etiologic relationship of parasites to these diseases, although he stated that he had seen the amebae of Lösch. His clinical descriptions are exceedingly clear and with the aid of the notes of autopsies, many of which were made by Dr. Joseph Leidy, one is enabled in many cases to make presumptive diagnoses of the type of dysentery present and to confirm them by the histologic and gross examination of the tissues from these autopsies still preserved in the Army Medical Museum. Woodward's classification is cited below as an evidence of the state of knowledge of this disease at that time and just preceding demonstration of the etiologic relationship of micro-organisms.

> The manifold varieties of these diseases may conveniently be grouped under the following heads:
>
> 1. *Acute Diarrhoea,* including the cases due to inflammation of the intestinal mucous membrane as well as those in which the intestinal lesion does not progress beyond simple irritation.
>
> 2. *Acute Dysentery,* including both the simple inflammatory and the diphtheritic forms.
>
> 3. *Chronic Dysentery,* under which head the cases reported during the war as chronic diarrhoea will also be included.
>
> 4. *Diarrhoea connected with tubercular ulceration of the intestines.*
>
> This classification is based chiefly upon clinical considerations. All cases of flux in which the frequent liquid stools are unaccompanied by marked tenesmus will be included in the first group; when tenesmus is a prominent symptom the cases will be assigned to the second; and the chronic fluxes will be grouped under the third, whether tenesmus be present or not; the fourth group is established for anatomical reasons, and includes those cases of diarrhoea, occurring chiefly among soldiers suffering from phthisis, in which there is tubercular ulceration of the intestines.
>
> The great majority of the fluxes observed during the war belong to the first three groups, and in the acute cases the distinction here made appears to be of some importance; for, whenever tenesmus was a prominent symptom, the disease was more severe and the danger to life greater. The chronic cases, however, whether tenesmus was present or absent, resembled each other in so many respects that it seems most convenient to consider them under a single head.
>
> A more detailed classification, based upon the anatomical lesions observed in autopsies, might appear desirable, but there are many difficulties in the way of such an undertaking. These difficulties will be encountered, whether the nature of the anatomical changes of the mucous membrane, or the portion of the intestine involved, be taken as the ground of distinction; during life it is not always possible to determine the former, and still more frequently it is impossible to fix the latter, so that no such classification would be of as much practical value to the military surgeon as the less ambitious one here adopted.

From that time to the present, the field has been dominated by the parasitologist, including the students of both protozoa and bacteria. This domination has been so great that differentiation based on clinical observation and the characteristic tissue changes produced by the various

parasites has been in abeyance and treatment for the most part has awaited definitive observations by laboratory examination. The consequent delay in the use of specific remedies has been responsible to a large degree for the failure of serum in the bacillary variety, and for a prolonged period of convalescence, due to the production of serious lesions which require considerable time to heal. Negative bacteriologic observations interpreted as positive protozoal evidence have resulted in the use of emetine in patients with bacillary dysentery who were toxic, febrile and not in any condition to receive ipecac or its derivatives. Physicians are now beginning to realize that the clinical picture and the evidences of the character of the process as presented to them, aside from the actual finding of the organism, are at least of as much value in determining treatment as the finding of the organism itself. Furthermore, they are available to us long before the bacteriologist can furnish a positive specific diagnosis, and if followed will be found to be accurate on presumptive evidence as often as, if not oftener than, the bacteriologic investigation.

The next twenty years saw considerable increase in the knowledge of dysentery. The ameba discovered by Lösch in 1875 was found in dysenteric ulcers in 1883 by Robert Koch, then a member of the Egyptian Cholera Commission. He described five cases of the disease, in four of which amebas were found in sections of the ulcers, as well as in the dejecta. Two of them were complicated by liver abscess, in one of which he found amebas in the "capillaries" of the abscess wall. This is the first record of the presence of these organisms in human tissue. Stimulated by the work of Koch, Kartulis, 1886-1891, described many cases of dysentery of both amebic and bacterial varieties, and designated them as endemic and epidemic, respectively. Kartulis was the first to describe amebas in the pus of a liver abscess and he noted that they were not present until the third day after operation. He gives the differential characteristics of the symptoms of the two types of disease and notes the infrequency of acute symptoms in the protozoal variety. He inoculated cats and produced the condition caused by *Entamoeba histolytica* as usually seen in this animal.

The term "amoebic dysentery" was introduced by Councilman and Lafleur in 1890-1891 as the result of their study at Johns Hopkins Hospital. Cassagrandi and Barbagallo (1897) differentiated fairly well the harmless and pathogenic amebas. Schaudinn, in 1903, introduced the names *Endamoeba coli* and *Endamoeba histolytica,* and it was believed for some time that he had definitely established the species differences, largely because of his dominant position in the protozoology of that day. His accounts were almost wholly erroneous, and it took many years to correct the conceptions formed as a result of his work. The distinctions were cleared up to a large extent through the work of

Walker and Sellards (1911), corroborated by that of W. M. James (1914). In addition to verifying previous work, Walker and Sellards' conclusions may be briefed as follows: Cultivatable amebas are nonpathogenic; *Endamoeba coli* is nonpathogenic; *Endamoeba histolytica* and *Endamoeba tetragena* are the same. The ingestion of cysts is apparently necessary to produce parasitism. The last conclusion is particularly important from the standpoint of epidemiology. The work of these scientists has been generally verified although, as was to be expected, endamebas have now been cultivated.

While much has latterly been written and many claims have been made with reference to the pathogenicity of various protozoal parasites, it cannot yet be stated that intestinal protozoa other than *Balantidium coli* and *Endamoeba histolytica* have produced pathologic lesions recognizable as such in the digestive tract of a human being.

In 1925, Boeck and Drbohlav successfully cultivated *Entamoebae histolytica*. With their methods and modifications, practically all the known species have been cultivated. Much additional information will undoubtedly be obtained from the study of endamebas in culture, while the use of this method in determining the presence of parasitization has already been found as efficient as and less laborious than concentration methods.

In 1897, Shiga reported the isolation of a bacillus in the bacillary dysentery epidemic in Japan (1896-1897). In 1900, Flexner found the Shiga organism, and also described another which he found more commonly in dysentery cases in the Philippines. During the early years of this century, various other organisms fairly closely allied to the Flexner type were described and others belonging to the paratyphoid-enteritidis group. From this time to the present, a great deal of work has been done on the bacteria found in clinical dysentery. The Shiga and Flexner organisms are successfully isolated in a relatively large proportion of cases caused by them if proper cultural methods are used and suitable, i. e., fresh, material can be obtained. Many outbreaks, clinically dysentery, have resulted in negative bacteriologic observations so far as these two groups are concerned, and the suspicion is always present that the bacteriologic method failed to discover the cause of the condition. Gradually we are becoming convinced that whereas the Shiga and Flexner groups produce a characteristic dysentery, other organisms (Salmonella group) under suitable conditions give rise to entirely similar pictures.

From a historical standpoint pathologists are not yet in a position to evaluate the relationship to dysentery of the various etiologic agents of bacterial nature. The Shiga organism forms a fairly constant group from both the bacteriologic and the serologic standpoints, though the recent work of Lacy indicates a serologic variation within this group the

importance of which has yet to be ascertained. Other recent interesting papers on the subjects of the variations of the Shiga-Flexner organisms are those of Morishima and Schobl.

Transmissible lysis of bacteria, the phenomenon described by Twort and D'Herelle, appears to be particularly applicable to the dysentery group and possibly will, in the future, influence methods of treatment either directly of itself or by rendering active immunization less difficult.

From the practical standpoint the most important recent development has resulted directly from the World War. As stated previously, definitive diagnosis by bacteriologic and protozoologic methods has been depended on, and the clinical picture and the pathologic anatomy of the disease as seen at autopsy, and as presented in the exudate in the stool during life, has been ignored or neglected. In the early years of the war it was believed that most of the dysentery in Mesopotamia, the Dardanelles, Egypt and other tropical and subtropical war zones was of amebic origin. The studies of Ledingham, Penfold and Woodcock, 1915, together with the work of Wenyon and O'Connor, published in 1917, and the work of Dobell over the same periods, resulted in establishing that the majority of these cases were not of amebic origin. The clearing up of mistakes in diagnoses in the British Army Expeditionary Forces, by Bahr and Willmore and Shearman, by means of a study of the clinical record and the exudate in the stools, and a clear exposition of the diagnostic value of the cell picture, established a diagnostic aid which has yet to be properly appreciated. The procedure of examining the cell exudate was carried further by Bahr and Willmore and Anderson, and verified by Haughwout in his observations on the differential diagnosis of dysenteries in the Philippines. Haughwout had not published his observations at the time Willmore and Sherman's paper appeared in the press, but he had arrived at similar conclusions. In addition, he initiated serum treatment on the basis of a presumptive diagnosis by this method with a favorable response. His results explained the variations in effectiveness of serum treatment heretofore observed. Presumptive diagnosis by this method being available within a few minutes after receiving a specimen, serum was given within a few hours of onset with as rapid clearing up of symptoms as is found in the early administration of diphtheria antitoxin. His results are controlled by cases of varying duration and they show definitely that the effectiveness of the dysenteric serum decreases with extreme rapidity after the first few hours of clinical symptoms. The value of this procedure as a differential diagnostic method is that it enables one to initiate specific treatment in the bacillary variety early, and that it prevents the use of ipecac in cases definitely not suited for it.

The cytologic picture in amebic dysentery is also characteristic but should not be used as an indication for specific treatment. In acute

amebic dysentery, only the finding of the organism itself, under conditions which indicate that it is the cause of the symptoms, justifies the use of ipecac. In the presence of *Endamoeba histolytica* in an exudate and under clinical conditions indicating bacillary disease, treatment should be administered as in a bacillary case, the amebic condition being left for a more appropriate time in the future.

The following paragraphs summarize the knowledge of the etiologic agents of dysentery, and the pathogenesis and pathologic anatomy of the lesions they produce, without direct reference to the literature in which the facts are recorded. The appended reference list covers practically all essential points.

PROTOZOA

Entamoeba histolytica is a tissue dwelling parasite of man which, under experimental conditions has produced lesions in laboratory animals but is not believed to be a natural parasite for other animals than man. It appears necessary in order to infect that the encysted stage be ingested (Walker and Sellards), though it is not proved that the trophozoite form is incapable of surviving the action of the juices of the stomach and infecting. It is believed that the cyst is in some way softened in the stomach and that the excystment takes place in the digestive tract below, probably in the lower part of the small intestine or upper colon, as the lesions are found in the latter organ and they rarely extend more than a few inches up the ileum.

The organism invades the tissue apparently by means of its digestive ferments, dissolving the cells of the intestinal glands along which it travels (fig. 1, *A*), finally making its way through the basement membrane and into the submucosa. Here it dissolves the tissue, multiplying, so far as is known at present, without encystment. There is little local response to the presence of the ameba. A few lymphocytes and endothelial leukocytes, a little edema and fibroblastic proliferation constitute the focal reaction to this parasite. The center of the mass is an area of necrosis with complete lysis of the tissue, and this detritus may be responsible for even the slight reaction found (fig. 1, *B*). Further extension of the lytic process finally leads to rupture onto the surface of the intestine, and the bacteria in the lumen are afforded an opportunity to enter the injured tissue. The method of spread of the amebas to other locations and the production of secondary lesions has not been determined. It is believed that the trophozoites expelled with the rupture of the focal lesion can reenter the tissue, but extension along lymph channels occurs and other foci may be thus formed in the submucosa without the necessity of entering the lumen of the bowel where conditions are less favorable for the continued existence of this parasite. The rapidity with which the amebic process progresses, and the char-

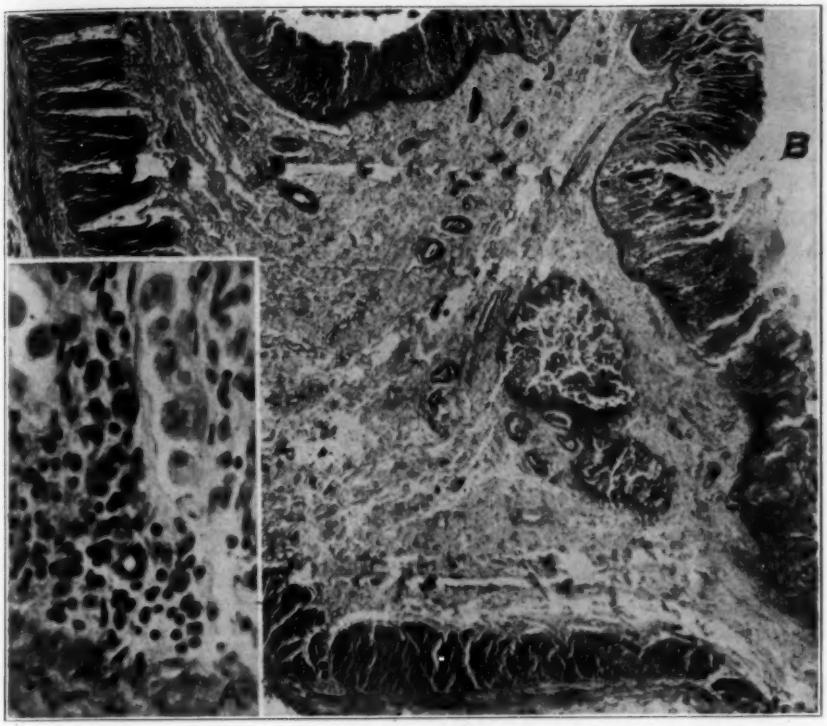

Fig. 1.—*A, Endamoeba histolytica* in gland of mucosa. *B,* amebic "abscess" in mucosa; the absence of leukocytic reaction should be noted.

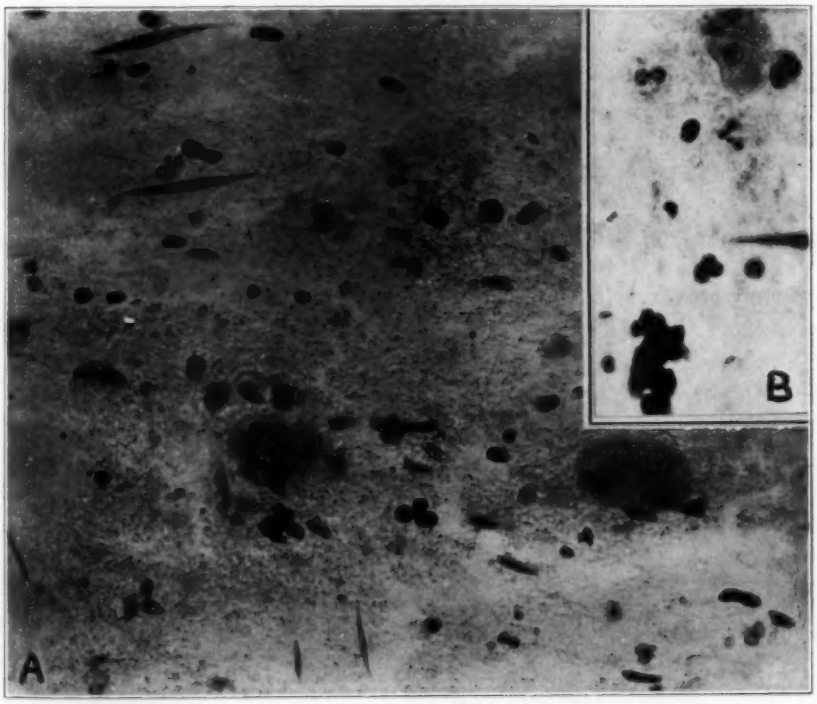

Fig. 2.—*A,* exudate in stool in early stage of exacerbation in amebic dysentery; the Charcot-Leyden crystals and leukocytic nuclei without cytoplasm should be noted. *B,* clumping of red cells and fading of leukocytic cytoplasm in same case as that shown in *A.*

acter of the lesions, vary as do the number of individual lesions and the anatomic structure involved. The sites of most frequent involvement are those in which the greatest stasis of intestinal content occurs—the rectum, cecum, sigmoid and flexures, respectively. The rapidity of penetration appears to vary with the number of amebas in the lesion, which in the more rapidly penetrating ulcers is enormous; yet no matter how numerous are the parasites there is little reaction aside from the lysis of the tissue, even though the muscle layer is rapidly dissolved and blood vessels opened. Such lesions are accompanied by considerable hemorrhage, and the ragged ulcers are filled with hemorrhagic slough. The presence of very few lesions in certain cases, over long periods, suggests that the parasite may not extend except under peculiar conditions of lack of resistance or anatomic accident. The cultivation of the parasite brings up the possibility that it may exist within the intestine without producing lesions, but careful clinical observation of so-called symptomless carriers will usually reveal some definite signs of present disease (Craig). The finding of cysts in the bile from duodenal tube drainage suggests the parasitization of the bile ducts of the gallbladder or the presence of small abscesses in the liver opening into the bile passages (Kofoid et al.). In this connection it is worthy of note that careful observation has now discredited the dictum that amebic abscesses of the liver are usually single.

As bacterial infection of the ulcer formed by the rupture of the submucous focus progresses the amebas become less numerous, at least as healthy appearing individuals, but are seen in the tissue surrounding and below the zone of inflammatory response. They make their way into the lymphatics and occasionally are found in the blood vessels of the submucosa. From both, the route of egress leads to the liver while from some of the lymphatics an entrance to the lungs may be gained. Lung abscesses except by extension through the diaphragm from the liver are relatively rare.

Amebas have been found in many locations in the body, most of which can be satisfactorily accounted for by the factors in the individual case, such as adhesions between bladder and rectum, but the evidence in favor of the conception that this parasite produces generally distributed infections is too meager to be accepted at present. Many of the clinical symptoms occasionally present in amebiasis are considered as due to the direct action of *Endamoeba histolytica,* when as a matter of fact they are probably due to pyogenic bacteria causing the secondary process, and are in every way similar to conditions produced in other secondary infections in the intestinal tract. The body responds with more or less characteristic symptoms to secondary infection, but with the possibility of some anemia from the loss of blood from vessels destroyed by the lytic action of the parasite, it is doubtful if *E. histolytica*

excites any general reaction on the part of the infected person. Suppurative lesions in the bowel afford an entrance to the circulation to whatever organisms are present and not only are the severe local reactions and the "dysenteric" symptoms due to secondary infection but also other symptoms such as joint and eye conditions may result just as they apparently do through ulceration or similar atria of infection elsewhere (respiratory tract, tonsils, teeth, etc.).

Secondary infection of the ulcers also gives rise to the symptom of dysentery which will vary in intensity according to the species of bacteria and amount of tissue involved. Ordinarily these are the organisms of little invasive power of the colon group, but streptococci may produce widespread phlegmon; the dysentery bacilli, the symptoms common to them and the anaerobic group, relatively common inhabitants of the human intestine, occasionally gain entrance through the ulcers and produce death rapidly with gas formation in the viscera. Symptoms thus vary to a marked degree and except for the milder infections treatment must be directed primarily to the secondary rather than to the primary cause. The ameba can safely be neglected during the interim. Such secondary conditions receive all too scant attention which is inexcusable today with the proved methods at hand to determine their presence. Furthermore, the treatment of the case is no more complete without clearing up these secondary infections than it would be without complete anti-amebic therapy. Too often a fatal termination or permanent invalidism results from the secondary process while the clinicians are concentrating their attention on anti-amebic treatment. Ulcerations still exist until all evidence of their presence has disappeared from the stools, and repeated examinations are necessary to determine this.

Aside from the presence of the amebas, without which a positive diagnosis should not be made, the exudate in the stool will vary widely. When much blood is present a definable exudate cannot be made out microscopically and amebas may not be found. Aside from such hemorrhage, the milder attacks or the early stages of many recrudescences are characterized by a rather characteristic cytologic picture in the stained smear from the stool.

When the initial amebic lesion ruptures onto the bowel surface, detritus, degenerated and normal trophozoites and some blood are discharged; but as practically no leukocytes exist at this period, few or none appear in the exudate. Symptoms calling attention to ulceration in the intestine do not occur until secondary infection has taken place. Bacterial infection causes leukocytes to appear in the tissues surrounding the abscess and to exude into the lumen. Varying numbers of amebas will also be present and the evidence of their action preponderates in the exudate seen in the stool. This is indicated by the appearance of the leukocytes, some 70 to 90 per cent of which consist of nuclei alone

(pyknotic bodies), the cytoplasm having been dissolved by the lytic action of the ameba (fig. 2, *A*). Red corpuscles, when in relatively small numbers, appear in clumps as if agglutinated (Anderson's phenomenon, fig. 2, *B*). Charcot-Leyden crystals are present in varying numbers and become less frequent as the leukocytic elements increase. Their origin and nature has not been determined. These crystals should not be considered diagnostic but they indicate the probability of amebic infection and the necessity for a thorough search, concentration of the stool and culture. Leukocytes, identifiable as such, show fading out of the cytoplasm without much change in the nucleus (fig. 2, *A* and *B*). As the purulent character of the secondary lesions becomes more pronounced, the proportion of pyknotic bodies decreases, but it will rarely be less than from 30 to 50 per cent of the basic staining elements. The exudate corresponds quite exactly with the pathologic picture in the ulcer above in which the piling up of granulating membrane occurs with superficial leukocytic infiltration and exudation of pus. Lytic action of the amebas somewhat deeper in the lesions results in recurrent breaking down of this low grade granulating membrane, so that the centers of the ulcers are constantly filled with necrotic material. Inflammatory reaction about the ulcer craters is relatively slight and depends on the nature of the invading bacteria. Mucosa intervening between ulcers appears essentially normal, except in those instances of phlegmon of streptococcus origin, or involvement in a bacillary dysenteric process. Phlegmon may continue to complete interruption of the circulation and gangrene of smaller or larger portions of the intestine. If sufficient intestine remains active to produce any bowel movement, extremely foul dejecta occur, while not infrequently, in fatal cases, the days just preceding death are marked by the absence of any bowel movement whatever and the true condition is not ascertained until autopsy. At this time greater or lesser areas of intestine will be found in an advanced stage of putrefaction so that their removal entire is difficult.

The clinical symptoms will also vary with the extent of the ulcerative process and its anatomic location. The more ulcerated surface there is present the greater will be the quantity of exudate appearing in the stool, and the greater the general reaction. Rectal ulceration will naturally give rise to some tenesmus from rectal spasm. Ordinarily, attacks are ushered in with few prodromes, while in the interims the patient is usually conscious that something is amiss in the abdomen, yet he rarely has acute discomfort. The blood shows relatively few changes, with the exception of anemia; this varies with the duration of the disease and is usually more severe than either history or symptoms would indicate.

Rather marked fibrous thickening of the intestine is consequent on the healing process and may constrict the lumen of the bowel. The con-

traction of this fibrous tissue by diminishing the blood supply seriously interferes with the healing of the ulcers.

The abscesses in the liver are of indolent type and may arise without definite symptomatic dysentery ever having been noted. The same type of lytic process goes on here as in the submucosa of the intestine. Usually the abscesses are surrounded by a considerable fibrous capsule and produce severe symptoms only as the result of secondary infection. Evidence of complete fibrotic replacement has been found in patients treated specifically for intestinal lesions.

Amebic abscesses in the lung are somewhat similar in type to those in the liver, are usually attended by considerable fibrosis and frequently are involved by secondary infection from the respiratory tract.

A drug has not yet been found to replace ipecac in the treatment of this disease. Recently, the arsenicals have been found to be of definite aid, while bismuth still has its place as an adjuvant treatment. In the anxiety to eradicate the condition by specific treatment, general tonic and supporting measures are too often neglected. One is usually dealing with a patient whose general condition is far below normal. Supporting measures and suitable diet are as much a part of treatment as is the use of specific drugs. Severe secondary infections giving rise to temperature and other evidences of intoxication should be alleviated before exhibiting ipecac, which, at such times, may give rise to untoward symptoms and definitely delay the recovery of the patient. Patients should not be discharged from observation until concentration methods and cultures do not reveal amebas in the stool, and until evidence of ulceration as shown by smears of the exudate has disappeared.

EPIDEMIOLOGY

The proportion of carriers of this parasite in the general population, according to reports presented, varies over a considerable range. In the temperate zones surveys indicate from 5 to 15 per cent; Kofoid and James report 53 per cent in a Colombian town where hygiene and sanitation though far from ideal were probably not worse than in many native tropical communities.

It is difficult to discuss the epidemiology of this condition. Satisfactory evidence is present to incriminate flies as a carrier from exposed fecal matter, but hands may be as important. The disease is characteristically an endemic condition, but what amounts to an epidemic will occur at any time, in any place, where the number of carriers is large, sanitary provisions are lax, and hygienic measures are not observed. Under such conditions, if large numbers of persons are exposed by means of fly-contaminated food, or food contaminated by carriers, a sufficient number of cases to cause an epidemic curve may occur. The apparent epidemic condition will be accentuated, if, as the result of

finding several cases, more careful examinations are made for the parasite. If the group examined has been exposed for some time before competent laboratory examinations are undertaken, the finding of cases may occur over a much shorter period than did the acquirement of the disease, and thus give rise to an epidemic curve. With the knowledge of the biology of this parasite and of the proportion of cases of dysentery which occur as the result of parasitism with this species, an epidemic would not be expected of the type seen in the bacillary form. One would expect to find a large number of cyst excretors in any group in which an epidemic outbreak of this disease occurred.

BALANTIDIAL DYSENTERY

Several morphologic types of balantidia have been described but the differences are of a minor order. The organisms fresh and stained from the intestinal tract of the pig and man are practically identical. It is not yet possible to evaluate the importance of this genus. If the organism of man is the identical species present generally in the pig one may anticipate an increasing number of clinical cases, which will not be more prevalent in any one climatic region, as swine are generally infected and cases are reported from every zone. Close contact with swine is usually demonstrated.

Balantidium coli is a large, free swimming ciliate having both a rotary and a forward movement, much like an auger or drill. Its cilia are larger than most bacteria. It enters the tissue by forcing its way between the gland cells of the mucosa of the colon, proceeds between the columnar cells and basement membrane and enters the submucous tissue, carrying with it greater or smaller numbers of bacteria. Aside from the trauma and secondary infection resulting from its stormy advent, the balantidium elicits little response on the part of the host. There is not any evidence of a lytic action, as seen in *E. histolytica* lesions, nor a cellular response indicating an inflammatory process, when the organism is well embedded in the tissue at a distance from suppuration. Characteristically, however, one sees islands of pus formation surrounding the *Balantidia* in the more superficial locations beneath the epithelium in which the organisms are apparently undergoing degeneration by karyorrhexis (fig. 3, *A*). Here, as in infections with *E. histolytica,* the secondary bacterial infection is not favorable to the parasite and they are found only in a morphologically healthy condition at a distance from purulent reaction (fig. 3, *B*). *Balantidium coli* is found in newly formed fibrous tissue laterally and beneath the purulent areas where the fibrosis aids in diminishing the circulation to the overlying mucosa. Submucosal abscesses and the fibrosis result in death of the mucosa without its solution, and it is then seen as a necrotic layer in which the glands retain their form but nuclei no longer

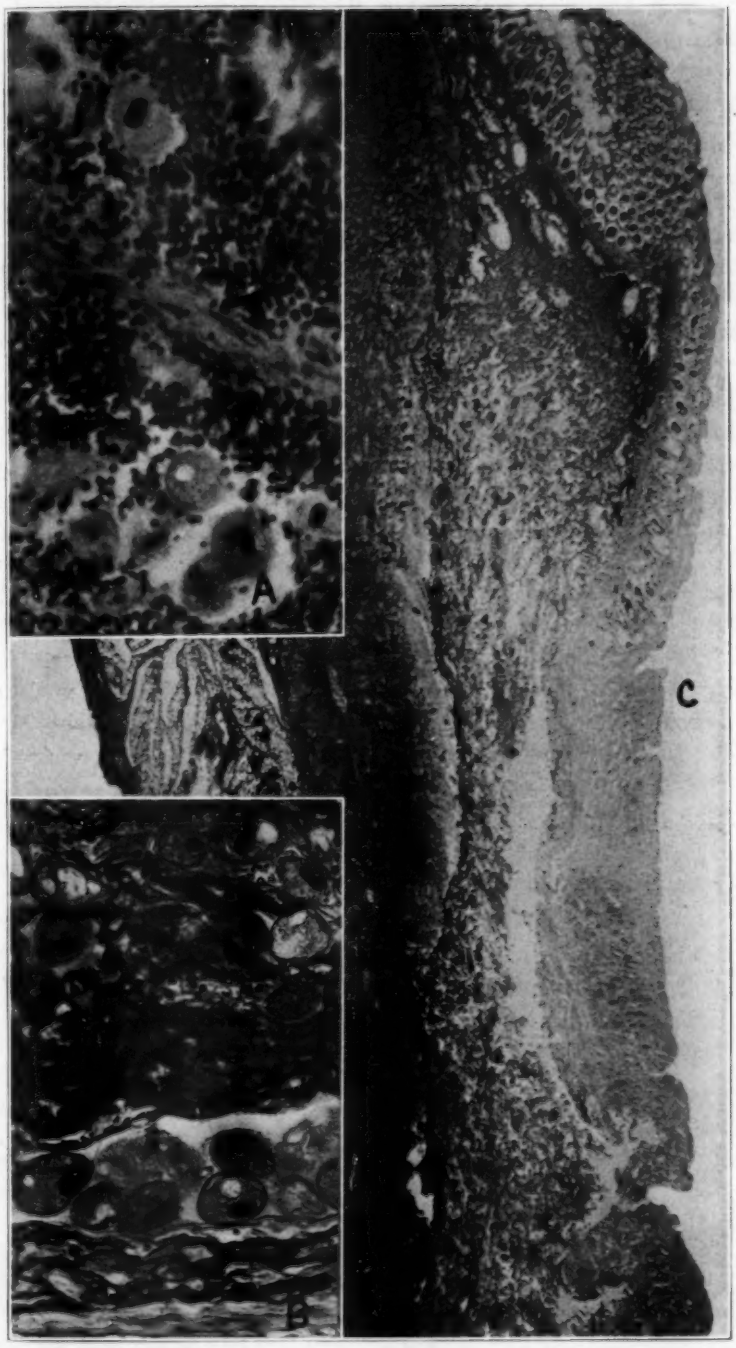

Fig. 3.—*A*, degenerated balantidia in abscess just beneath mucosa. *B*, relatively normal balantidia in dense connective tissue just above muscularis. *C*, balantidial lesion just before separation of necrotic mucosa.

stain (fig. 3, *C*). These necrotic masses appear grossly as opaque pale areas and when sloughed off leave shallow ulcers based on the sclerotic submucous tissue. The edges are ragged from strands of mucosa projecting where the necrotic mass separated. Small blood vessels are ruptured giving rise to hemorrhage while balantidia in the superficial layers are thrown off and appear in the stool. Secondary ulcers are formed by reinvasion from the lumen of the intestine and probably also by extension.

Grossly, in the well developed case, the colon presents numerous shallow blood stained ulcerations with ragged edges and little inflammatory reaction between, while the intestinal wall is thickened and indurated.

In the early stages, the exudate, as would be expected from the foregoing, presents a few *Balantidium coli,* some of which are degenerated, and a few leukocytes. The latter show few signs of nuclear change and no evidence of lytic phenomena. Soon, as the result of secondary infection, the number of leukocytes increases until the field is practically all pus with the number of balantidia relatively decreased, though these organisms are rarely abundant.

The clinical picture resembles many cases of amebic disease. As in amebic dysentery, the subjective symptoms vary with the variety of organism which secondarily infects the ulcerations. Early in the disease blood is found in considerable quantities in the stool, which later becomes more purulent. Exacerbations and remissions are described. Parasitization without symptoms has been found in man and is the usual condition in the pig. The diagnosis is easily made by finding the organism.

Treatment.—In his first case Malmsten succeeded in relieving the symptoms by local treatment of the rectal ulceration. In his second case treatment was not of particular value. Various drugs have been tried with indifferent success. Within the last year Aguilar has reported excellent results with stovarsol.

INTESTINAL FLAGELLATES

Giardia, Trichomonas, Etc.—Flagellates are frequently found in diarrheal conditions when the evidence as presented indicated a strong probability that these organisms were responsible. Giardia has been reported within the tissue and attached to gland cells. It has more claim to definite pathogenicity than any others of the group. The flagellates are not usually found in the stool except under conditions of rapid emptying of the intestine as occurs after the ingestion of cathartics or foods irritant to the intestine. Under these conditions they are washed down and may be present in large numbers. Under normal conditions

too few reach the stool to be recognized. Parasitism with giardia is most accurately determined by means of the duodenal tube and it would seem that they also colonize in the gallbladder and possibly in the bile ducts. Many of the cases reported as caused by these organisms have also presented other conditions which were much more likely to have been the true etiologic factors. The results of treatment have been too rapid in the majority of reports to coincide with the usual difficulty in eradicating such organisms and have been so varied that it seems unlikely that protozoa usually requiring more specific therapy could be eliminated so easily. Trichomonas have been seen to ingest red cells. This occasionally observed phenomenon to my mind does not brand them as pathogenic any more than the finding of bacteria in *Endamoeba histolytica* frees it from such condemnation. The etiologic relationship of the flagellates to lesions in the human intestine has not been satisfactorily demonstrated. Fairise and Jacquot describe giardia in the tissues in one case. Pathologically, their description is of a chronic ulcerative colitis resembling amebic disease with diverticula-like areas. Giardia were seen in tissues as cysts and free forms. While it is difficult to judge without examining the tissues their description suggests that the organisms were included in the bases of ulcerations rather than that they were invasive. It does not seem reasonable that flagellated organisms whose habitat as indicated by their anatomy is normally fluid should have tissue invasive power.

BACILLARY DYSENTERY

Organisms: *B. dysenteriae,* Shiga and Flexner groups. These are the typical dysentery bacilli, but clinical dysentery is also produced by the genus *Salmonella* (food poisoning group) and the more important members of this group with reference to the production of the syndrome are *B. paratyphosus* "B," *B. aertrycke*—though this organism occasionally produces typhoid-like symptoms—*B. typhi murium, B. enteriditis* of Gaertner, *B. morgani* and *B. suipestifer,* Kruse. This *Salmonella* group is found in those infections of the intestinal tract resulting from the ingestion of these organisms with contaminated food. *B. typhi murium* is a particularly important organism because of its frequent presence in mice and subsequent contamination of food.

Pathologic Anatomy.—Bacillus dysenteriae, Shiga, produces both an exotoxin and an endotoxin. Injection of the toxin of either this or the Flexner organism will give rise to dysenteric-like lesions in the intestine. The primary change in such experimental work is an edema and hyalin degeneration of the submucosa, which will eventually lead to a necrosis of that membrane. The organisms are positively chemotactic for leukocytes, and they produce an acute inflammatory reaction of varying

intensity. The absorbed toxins have an affinity for joint membranes and the soluble toxin of the Shiga organism produces degeneration in the nervous system.

In the mildest cases there is a swelling of the solitary follicles and more or less injection of the entire mucous membrane. In fact, involvement of the whole mucosa in bacillary infections and the lack of such involvement in amebic infections is a valuable differential diagnostic point. Small ulcers are produced in the follicles even in the milder attacks which clinically may be of relatively short duration. As a rule in Shiga infections and in a considerable number of the Flexner types there is a more diffuse process over the entire mucosa which shows in order, intense reddening, swelling, a necrosis of the superficial layers, more or less hemorrhage and the formation of diphtheritic membrane. The intensity is particularly pronounced over the projecting folds of the mucosa where usually the first necrotic areas are seen and where ulcers, after the casting off of the slough, usually appear. Primarily, at least, the lesions do not extend to the muscularis, though later perforations may occur, probably as a result of secondary infection. Polymorphonuclear leukocytes early enter the field, and varying numbers of macrophage cells are present. As the disease progresses the macrophage cells become less numerous, polymorphonuclears increase and shreds of necrotic membrane are cast off into the lumen of the intestine.

In the early stages of the generalized process one sees a marked general infiltration with leukocytes with considerable inflammatory edema. In the upper layer masses of leukocytes are enmeshed in fibrin; below this are some fibrin, leukocytes and many macrophages while the latter cells are diffusely scattered in greater or lesser numbers throughout the submucosa. Leukocytes are less abundant as one approaches the muscle layer, but they are still relatively numerous and can be seen escaping from the blood vessels of both the submucosa and the subserosa. In the older ulcers after the acute process has ceased, considerable connective tissue is seen forming at the base; granulation tissue projects into it, while new formed epithelium projects over the edges. These ulcers are relatively slightly undermined and their edges are ragged rather than rounded at first, only becoming smooth when the healing process is fairly well advanced.

Dysentery organisms are apt to disappear early from the dejecta. Their total time of acute action is in most cases relatively short. When the infection ceases to progress the ulcers gradually fill in, the more rapidly the more bland the intestinal content is kept, from both the physical and the chemical standpoints. Considerable scarring and thickening may result from this reparative process. All degrees of intensity are found, and varying amounts of mucosa are affected in the different cases. Mild infections can be aborted by the simple use of

cathartics though the actual pathology can only be surmised by careful examination of the exudate in the stools.

Diagnosis.—The exudate: In the earliest stages, which are rarely seen, the first cells to appear are mononuclears and represent the throwing off of these cells normally found in considerable number in the superficial mucosa. Quickly, the exudate becomes purulent and contains greater or lesser numbers of macrophage cells, many of which ingest leukocytes and erythrocytes. The leukocyte picture is fairly constant and shows a toxic degeneration of the nucleus, characterized by the condensation of basophilic particles around the periphery in ringlike arrangement in each of the lobes of the nucleus. The cytoplasm shows little change, but it may contain organisms. The macrophage cells show evidence of degenerative changes by pyknosis and fragmentation of their nuclei, and in a well established case macrophages are found in which only remnants of basophilic material remain, outlining the periphery; so-called "Ghost cells" (fig. 4).

Considerable numbers of fat droplets are seen both in the leukocytes and in the macrophage cells. These appear as highly refractile bodies in a fresh preparation. As the disease progresses favorably, the leukocytic content becomes less marked. Bleeding, which was present in greater or lesser quantities in the early stages, decreases. Macrophage cells disappear, and the leukocytes show less of the toxic degenerative changes. The important point to remember is that ulcers have not healed until all exudate has disappeared from the stool.

Evidence of continuation of lesions is presented usually in mucous attached to scybalous masses of fecal material, when such are allowed to occur, and characteristically these masses show in strands of mucus greater or lesser numbers of partially digested leukocytes and single cells or small bits of mucous membrane rubbed off the edge of the unhealed ulcers.

Specific diagnosis by bacteriologic methods should be carried out whenever possible, as in this way alone can the etiology be learned and the epidemiology ascertained. Its results are presented too late to be of much value in treatment. The methods will not be discussed here. The Shiga organism and the Flexner group offer little difficulty in diagnosis. The *Salmonella* group is extremely difficult, and little of value, so far as diagnostic procedure is concerned, has come to attention of recent years. Absorption tests must be utilized for the ultimate species differentiation.

Clinical Picture.—In infection with the Shiga and Flexner organisms fairly typical pictures are produced which vary greatly in intensity. It is an acute infectious disease characterized by fever, leukocytosis, more or less prostration and relatively acute gastro-intestinal symptoms, vomiting, nausea, abdominal pains, cramps and tenesmus. Some

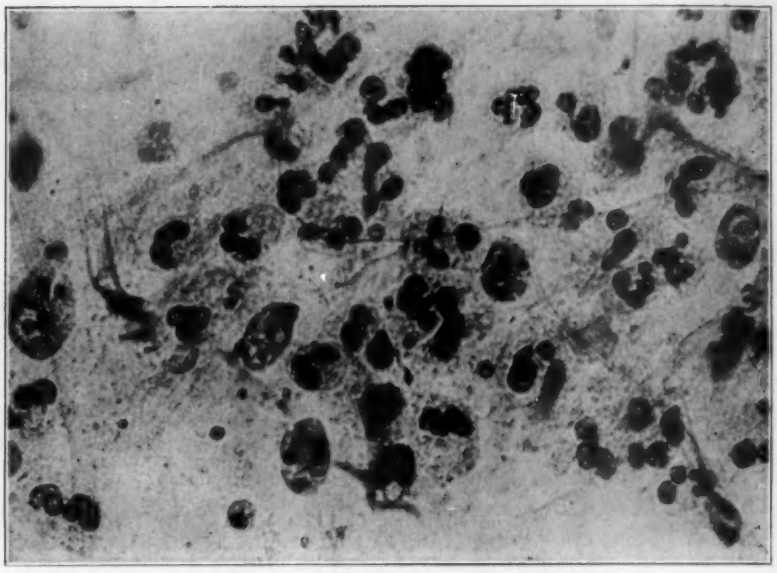

Fig. 4.—Exudate in bacillary dysentery.

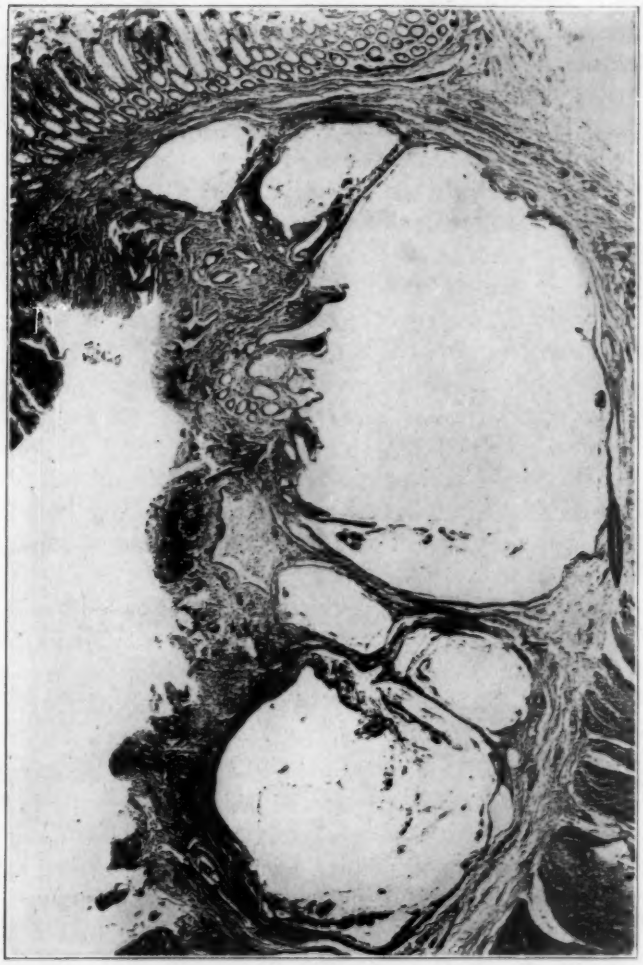

Fig. 5.—Cyst at base of ulcer, following bacillary dysentery.

bacillary dysenteries caused by the Flexner type of the dysentery bacillus run a relatively afebrile, nontoxic course and may, therefore, easily be mistaken for amebic dysentery. If treated on this basis by anti-amebic methods not only may the bacillary process proceed unchecked to what may be a fatal outcome, but also the administration of emetine to a toxic patient may bring about serious cardiac symptoms. In a measure, however, this is the most dangerous type of dysentery. A fulminating case, by reason of the violence of the symptoms and the extreme toxemia, dehydration and exhaustion, leaves the patient in such physical condition that his after-care is given especial attention. In the milder cases, the patient may feel perfectly well in a few days, and then he is prone to leave his physician and resume his usual mode of life and diet before the ulcers in the colon have healed. These cases should be carefully checked at intervals for several weeks, and the slightest evidence of suppuration should call for prompt and strict regulation of the diet and stools.

In the fulminant types of bacillary dysentery the need for speed in diagnosis and treatment is imperative. The clinical picture is dynamic in the extreme. There may be scarcely any premonitory stage, the patient becoming acutely ill almost at the start. In some instances the symptoms are choleraic, the patient passing large, serous, bloodstained stools and showing symptoms of dehydration almost from the beginning. In other instances, he may pass into a stage of profound intoxication and collapse, dying without having passed a dysenteric movement. Such cases require quick and heroic treatment. Intravenous and subcutaneous injection of physiologic sodium chloride solution should be pushed vigorously in an effort to keep down blood concentration.

Treatment.—The efficacy of treatment varies inversely as the duration of the disease. In fact, specific treatment should be used within the first few hours as its efficiency after ulceration has occurred is extremely low. Microscopic examination of the stools should govern the primary serum treatment and the diet throughout the course and during convalescence.

Postdysenteric Ulceration.—So long as ulcerations remain in the intestine, exudate will be found, if the material is properly examined. The symptoms will depend on the amount of intestine affected, which varies with the intensity and duration of the disease before proper treatment was instituted.

The chronic dysenteries are usually prolongations of attacks improperly treated, or untreated cases so mild in the early symptoms as to escape recognition. In some cases dysentery bacilli are still found. As Woodward has clearly shown in his treatise, there occurs during the healing process in some cases, a closing in of the ulcers leaving islands of mucous membrane in the bases which form cysts projecting above the

surface (fig. 5). Because of the relative lack of blood supply to the intestinal surface of these cysts, these occasionally necrose or become traumatized and broken, freeing their contents into the lumen of the intestine, and forming small ulcers. Since the discovery of organisms such lesions have been definitely proved to contain dysentery bacilli. The treatment of these conditions is dietetic with the use of saline aperients and should be persisted in until all evidence of ulceration has disappeared.

Bargen of the Mayo Clinic has described a number of cases of a chronic type of dysentery from which he has isolated a streptococcus. This organism produced definite dysenteric lesions in the intestine of experimental animals and was again isolated from the lesions. Further work should be done on this type of infection. Some other workers (Hurst) have not been able to verify Bargen's work with reference to etiology.

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Notes and News

University News, Promotions, Resignations and Appointments.—Lloyd Arnold has resigned as professor of pathology and bacteriology in the Loyola University School of Medicine, Chicago, and has been appointed associate professor of bacteriology and preventive medicine in the University of Illinois.

David Willis has been appointed instructor in the department of pathology and bacteriology in the University of Illinois.

The pathologists to various London and provincial hospitals have organized the British Pathologists' Association "to develop the application of pathology in relation to medicine and to protect the interests of those engaged in its study and practice."

Myron L. Stringer has been appointed instructor in pathology and Edgar D. Shanks instructor in bacteriology in Emory University School of Medicine, Georgia.

The senior class of the medical school at the University of Pennsylvania has presented a portrait of the late Dr. Allen J. Smith, who was professor of pathology and also dean of the medical school.

A painting of Walter Reed has been unveiled at the George Washington University Medical School. At the time of his epochal work in yellow fever, Walter Reed was a member of the faculty of this school.

A gift of $100,000 has been made to the Albany Medical College as a memorial to Dr. Cyrus Strong Merrill by his daughter, Mrs. James Monroe Lown, endowing the professorship of pathology.

Imre Dobos, pathologist at St. James Hospital, Butte, Mont., has been appointed to the staff of the Colorado State University School of Medicine at Denver, and will assume his duties shortly. Dr. Dobos is a graduate of the University of Vienna, and came to Butte about five years ago.

The department of bacteriology in the school of medicine of Vanderbilt University has been organized with James M. Neil as professor, Roy C. Avery as assistant professor, William L. Fleming, John Y. Sugg and Luverne Harris as assistants. Emedio L. Gaspari is fellow on the Denison fund.

N. Paul Hudson has recently been appointed to the Field Staff of the International Health Board and begins active service April 1, 1927, Dr. Hudson worked under the direction of E. O. Jordan at the University of Chicago where he did part of his medical work. He was graduated from the Harvard Medical School and for the last eighteen months has been at the Boston City Hospital under Frank B. Mallory.

Death of Thomas S. Pigg Strangeways.—Thomas S. Pigg Strangeways, Huddersfield lecturer on special pathology in the Cambridge University and director of the Cambridge Research Hospital, who made extensive investigations of arthritis and was an expert in tissue culture, died on Dec. 23, 1926. A memorial fund is in process of formation, the first object being to provide scholarships for his five sons.

Biological Abstracts.—Number 1 of this journal has appeared. *Biological Abstracts* aims to be a comprehensive abstracting and indexing journal of the world's literature in theoretical and applied biology, exclusive of clinical medicine. The following are editors of sections of special interest to pathologists:

E. W. Goodpasture, morbid anatomy; G. H. Whipple with R. P. Kennedy, functional pathology; S. Bayne-Jones, immunology; George H. Smith, filtrable viruses, bacteriophage, etc.; R. W. Hegner with W. W. Cort and F. M. Root, animal parasitology; James S. Simmons and I. S. Falk, medical and public health bacteriology, respectively. The publication office is at Menasha, Wis., and the editorial office at the University of Pennsylvania.

William Wood Gerhard Gold Medal Awarded.—The William Wood Gerhard Gold Medal of the Philadelphia Pathological Society was awarded on April 21, 1927, at the Annual Conversational Meeting of the Society, to Theobald Smith, director of the department of animal pathology of the Rockefeller Institute for Medical Research. Dr. Smith delivered the Annual Conversational Lecture on that date, the title being, "The Passing of Disease from One Generation to Another and the Processes Tending to Counteract It." The Gerhard Medal of the Philadelphia Pathological Society was established in 1925 to be given as an award for eminent work in pathology.

Abstracts from Current Literature

Pathologic Physiology

Urea Retention. P. S. Hench and M. Aldrich, Arch. Int. Med. **38**:474, 1926.

The presence or absence of urea retention in body fluids can be determined by the estimation of the mercury combining power. The mercury combining power of blood is defined as the number of cubic centimeters of 5 per cent solution of mercuric chloride capable of combining with 100 cc. of deproteinized blood. The normal values vary between 70 and 100. The blood urea can generally be estimated from the mercury combining power by use of a simple formula. The mercury combining power of serum and plasma are approximately equal, though lower than the mercury combining power of whole blood. The urea or serum and plasma can also be approximated by formula. The mercury combining power of the blood in polycythemia and leukemia varies with the total nonprotein nitrogen rather than with the blood urea, on account of the abnormal composition of the blood in such cases. The mercury combining power of the serum or plasma or of the saliva (the salivary urea index) is not so affected, and may be used for the estimation of the urea. Five cubic centimeters of oxalated blood is added drop by drop to 5 cc. of 10 per cent trichloracetic acid in a centrifuge tube and centrifugalized for five minutes. Five cubic centimeters of clear protein free filtrate is titrated with a 5 per cent solution of mercuric chloride. The mercury solution is added to the buret until a test drop of mixture when added to drop of saturated sodium carbonate on porcelain spot plate gives a reddish brown precipitate within three seconds.

S. A. Levinson.

Peristalsis in a Loop of Small Intestine. L. E. Hines and H. C. A. Mead, Arch. Int. Med. **38**:536, 1926.

A man with congenital umbilical hernia containing a single loop of small intestine was used for the study of intestinal movements. Active peristaltic waves were present in 89 per cent of hunger periods and in 19 per cent of nonhunger periods. Reverse peristalsis was observed consistently during periods of active movement. It was probably normal in the small intestine. Active progressive and reverse waves were not usually associated with pain, but tonic spastic contractions were always accompanied by violent colicky pain. The tonic contractions occurred twice during periods of diarrhea and once when hunger was the only complaint. Active intestinal movement was initiated by inflating an intragastric balloon. Intestinal movements were apparently neither inhibited nor accelerated during sleeping periods.

S. A. Levinson.

The Metabolism of Normal and Malignant Cells. James A. Hawkins, J. General Physiol. **9**:771, 1926.

From a repetition and extension of Warburg's work on anaerobic glycolysis in malignant tissues, the writer concludes that the glycolytic activity of a tissue is a function of its rate of growth, and that from this activity a classification of tissues may be made more closely corresponding to their biologic status than from the aerobic glycolysis-respiration ratio used by Warburg for this purpose.

H. E. Eggers.

SIGNIFICANCE OF CHANGES IN COMPOSITION OF BLOOD AND URINE AFTER INGESTION OF GLUCOSE. I. KATAYAMA, J. Lab. & Clin. Med. **11**:1024, 1926.

Feeding 1.75 Gm. of dextrose per kilogram of body weight in 50 per cent solution to twenty-two normal and hyperthyroid subjects produced in the majority a drop in the inorganic phosphorus of the blood, with a marked increase in output in the urine. The release of the phosphate combined as hexos phosphate when the hexos is converted into glycogen is a possible explanation of the increased phosphorus excretion. A decrease in blood and urine chlorides also noted in a majority of cases was thought to be a result of shifting of the chloride from the blood to other tissues. It was found that an increase in lactic acid in the blood occurred coincidentally with the hyperglycemia, although those cases showing lowered tolerance for carbohydrate presented less change in the lactic acid content than those with normal or increased tolerance.

RUTH TAYLOR.

ON THE PROCESS OF LYMPH FORMATION. M. KAYUMI, J. Lab. & Clin. Med. **11**:1117, 1926.

Endothelial cells of capillaries and glomeruli are stimulated by a second class of lymphagogues causing a marked increase in urine output and lymph flow. The first class of lymphagogues promotes the migration of tissue fluids into the lymphatic system. The urine output increases because of the passage of the tissue fluids into the circulation through the lymphatics. It does not increase so much following the second class which stimulates secretion in the kidney. Pituitary extract inhibits the secretion of endothelial cells of both blood capillaries and glomeruli, the lymph flow, the blood concentration and the urine output decrease; but the urine output increases soon after the stimulus of the hydremia is heightened. The author is of the opinion that substances which are like lymphagogues appear in lymph spaces as products of metabolism. Some increase tissue fluids, attracting water from the tissue cells and blood; others promote the migration of tissue fluids into lymphatics. Hence, lymph flowing out of the thoracic duct may contain excretions produced by metabolism of tissue cells; Kayumi believes that the cellular physiologic theory may be true, but that the lymphagogues increase functions of organs is a theory with objectionable points. The blood capillaries act to the same purpose as glomeruli; the latter carrying substances out of the body, the former sending them into lymph spaces. The author believes that these capillaries may be called "pre-glomeruli."

S. A. LEVINSON.

THE ANTIKETOGENIC INFLUENCE OF INSULIN IN DIABETES MELLITUS. J. A. KILLIAN, J. Lab. & Clin. Med. **11**:1132, 1926.

The administration of insulin in cases of diabetes mellitus results in an immediate decrease of the ketone bodies of the blood and urine, reaching the maximum in from four to six hours. The decrease in the ketosis is accompanied by a corresponding rise in the alkali reserve of the blood plasma. The rise in the carbon dioxide capacity is associated with a proportional increase in the blood plasma p_H. The antiketogenic influence of the insulin apparently is due to the more complete oxidation of the carbohydrates stimulated by the substance.

S. A. LEVINSON.

EFFECT OF GLUCOSE ON TOLYLENEDIAMINE ICTERUS. A. v. KÁLLÓ, Beitr. z. path. Anat. u. z. allg. Pathol. **75**:420, 1926.

Recent experimental work has furnished conclusive proof of the extrahepatic formation of bilirubin. If a dog with the liver completely excluded from the circulation is kept alive sufficiently long, there develops not only bilirubinemia but also actual tissue jaundice, as shown by Mann and Magath. There are still, however, upholders of the older Minkowski doctrine, "ohne Leber keinen Icterus." Thus Melchior, Rosenthal and Licht, using the method of Mann and Magath, admit the extrahepatic formation of bilirubin and the development of tissue pigmentation, but claim that the amount of bilirubin formed is not great enough to cause jaundice and that the tissue pigmentation which develops in the Mann-Magath experiment is due to a lipochrome. In a further attempt to establish the necessity of the liver for the development of jaundice, they claim that icterus does not develop after poisoning by tolylenediamine in dogs prepared by the Mann-Magath method. Since, in this method of experimentation, it is necessary to use dextrose intravenously to keep the animal alive, von Kálló investigated the effect of intravenous dextrose injection on tolylenediamine icterus in dogs with the liver intact. Dextrose alone did not cause increase in the bilirubin of the blood. It did, however, completely prevent or markedly delay the development of icterus following tolylenediamine. Von Kálló, therefore, concludes that the objections of Melchior, Rosenthal and Licht to the extrahepatic formation of bilirubin in the hepatectomized dogs content of the tissues or even increase it.

O. T. SCHULTZ.

INSULIN AND TISSUE GLYCOGEN. H. EDELMANN, Beitr. z. path. Anat. u. z. allg. Pathol. **75**:589, 1926.

In guinea-pigs, large doses of insulin caused the disappearance of glycogen from the liver, skeletal musculature and myocardium, whereas smaller doses, although they caused a decrease in the blood sugar, did not change the glycogen are not valid.

O. T. SCHULTZ.

THE ORIGIN OF THE CEREBROSPINAL FLUID. F. K. WALTER, Deutsche Ztschr. f. Nervenh. **90**:161, 1926.

The intraventricular fluid was found to differ in chemical composition from the subarachnoid fluid. The author believes that the fluid arises from the entire brain surface, the capillaries and the nerve parenchyma, and flows to both ventricular and outer surfaces.

ROY GRINKER.

STUDIES ON THE PERMEABILITY OF THE MENINGES. F. WALTER, Deutsche Ztschr. f. Nervenh. **93**:1, 1926.

Increased permeability of the meninges were found in 90 per cent of cases of general paralysis and in no case of metencephalitis.

ROY GRINKER.

EXPERIMENTAL STUDIES OF THE INTERNAL SECRETION OF THE PANCREAS. PART 4. ON THE PANCREATIC HORMONE IN THE BLOOD IN DIFFERENT CONDITIONS. PART 5. INTERNAL SECRETION OF THE PANCREAS, AND THE VAGUS NERVE. TOGO HOSHI, Tohoku J. Exper. Med. **7**:422, 445, 1926.

The method preferred for the isolation of the pancreatic hormone from the blood used picric acid and acetone mixed with defibrinated blood. The hormone

content of the blood of a starved rabbit remained practically constant through from one to five days; was little affected or slightly decreased by injections of pilocarpine or pituitary extract; tended to decrease slightly after thyroid feeding, and was increased by injections of epinephrine hydrochloride.

From previous reports and from his own investigations including determinations of the blood content of the pancreatic hormone as influenced by stimulation of the vagus, the author concludes that the splanchnic nerves alone govern the epinephrine secretion, and that the vagus nerve alone governs the pancreatic internal secretions. The blood content of this secretion was uninfluenced by splanchnicotomy.

E. B. PERRY.

ON THE EFFECTS OF AFFERENT STIMULATION OF THE VAGUS NERVE ON SOME VEGETATIVE ORGANS. KASANU TASHIRO, Tohoku J. Exper. Med. **7**:509, 1926.

Centripetal stimulation of the vagus nerve, if strong, raises the blood pressure (except in animals with splanchnic nerves cut, with viscera removed or under deep anesthesia even with both vagi cut, and in them the blood pressure is lowered), and inhibits the movements of the stomach and intestines; if weak, it lowers the blood pressure and accelerates gastro-intestinal activity; and regardless of intensity it lessens the rate of heart beat and depresses respiration. These changes may be considered reflex phenomena similar to those caused by sensory nerve stimulation.

AUTHOR'S SUMMARY (Condensed).

Pathologic Anatomy

BLOOD CHANGES IN THE ANTEPARTUM AND THE POSTPARTUM PERIOD OF YOUNG MOTHERS. I. HANDELMAN, A. ROSE and C. P. SHERWIN, Arch. Int. Med. **37**:725, 1926.

The calcium concentration during gestation was normal, with a slight decrease immediately after parturition and a rise to high normal just before dismissal. Pregnancy did not alter the phosphorus content of the blood of the group studied, nor was there any change during the postpartum period. High normal concentrations of creatinine were found in the blood during the antepartum and the postpartum periods. The output of creatinine in the urine was increased during the fetal formation but returned to normal immediately on parturition.

S. A. LEVINSON.

STENOSIS OF THE ISTHMUS (COARCTATION) OF THE AORTA AND ITS DIAGNOSIS DURING LIFE: REPORT OF FOUR CASES. JOHN T. KING, JR., Arch. Int. Med. **38**:69, 1926.

In the four cases of stenosis of the isthmus (coarctation) of the aorta recognized during life reported, two were thought to be instances of slight stenosis, two of well marked stenosis or total obliteration of the aorta at about the site of the entrance of the ductus botalli.

Postmortem reports show that the condition is rarely recognized during life. Coarctation occurs more often in males than in females; it occurs at any age after birth, and is compatible in some cases with long periods of hard physical work. Symptoms that may occur are palpitation, dyspnea, myocardial insufficiency, nocturia, cramps in the legs and intermittent claudication.

The signs that may occur are: (*a*) Bilateral pulsation in the interscapular region. This is the most important physical sign; the pulsation progresses

from above downward. (*b*) Relatively greater pulsation in the upper extremities than in the lower. (*c*) Pulsating, superficial, collateral arteries, coursing obliquely across the back of the thorax downward toward the spine. Dilated intercostal arteries. (*d*) Relatively higher blood pressure in the arms than in the legs. (*e*) Tendency to higher blood pressure in the right than in the left arm. (*f*) Pulsus differens, due to the relative delay of the apex of the left radial pulse and rounding of its apex. (*g*) Tendency for the right radial pulse to feel larger than the left. (*h*) Systolic murmurs over areas of interscapular pulsation, over the collateral arteries, at times over the arch of the aorta anteriorly or over the whole aorta posteriorly. [The bibliography of this article includes 222 titles.]

AUTHOR'S SUMMARY.

MYCOTIC ANEURYSM OF THE AORTA. F. M. SMITH and G. H. HANSMANN, Arch. Int. Med. **38**:367, 1926.

The case reported showed clinical manifestations of subacute bacterial endocarditis in which *Streptococcus viridans* was the responsible organism. The course of the disease was rapid and it was terminated by the rupture of a mycotic aneurysm. Two hundred and seventeen such cases are reported in the literature. This type of aneurysm is seldom recognized during life, because of the small size and the frequent location in the root of the aorta.

S. A. LEVINSON.

LIPOID NEPHROSIS. F. D. MURPHY and L. M. WARFIELD, Arch. Int. Med. **38**: 449, 1926.

The author's cases and Epstein's description of chronic nephrosis are examples of Munk's lipoid nephrosis. Murphy and Warfield believe that the disease is a tubular lesion and can occur without any glomerular inflammatory lesion, as far as methods of examination reveal. Polarscopic examination of the urine sediment will help to reveal such cases. The cause of the disease is obscure but may be due to a disturbance of metabolism of the colloids. The prognosis in most cases is good.

S. A. LEVINSON.

EFFECTS OF LIGHT ON NORMAL RABBITS, WITH ESPECIAL REFERENCE TO THE ORGANIC REACTION: I. CLINICAL AND POSTMORTEM OBSERVATIONS. II. ORGAN WEIGHTS. III. ANALYSIS OF ORGAN WEIGHTS. LOUISE PEARCE and CHESTER M. VAN ALLEN, J. Exper. Med. **44**:483 and 502, 1926.

I. A group of fifty normal male rabbits kept under conditions of constant light that had none of the shorter ultraviolet rays and another group kept in constant darkness for from two to twelve weeks were observed clinically and subjected to postmortem examination for the purpose of determining the effect of these environmental conditions on general body health and the weights of organs. A similar group of fifty rabbits caged in an ordinary animal room, for the same period, and two groups of forty and twenty rabbits, respectively, which had recently been brought into the laboratory, served as controls.

The general health of the rabbits was not impaired by the artificial light or by the exclusion of light. The gain in body weight which occurred in all groups was especially marked in the case of those kept under conditions of constant light.

The incidence of spontaneous disease recognizable clinically during the experiment was extremely low and of a mild character and did not obviously

disturb the health of the animal. It was found at postmortem examination, on the other hand, that 59.3 per cent of the rabbits caged indoors, that is, in the light, dark or unaltered rooms, and 58.3 per cent of those recently brought to the laboratory, had visible lesions of some kind. The great majority of these lesions, however, were of a slight grade, and none appeared to have any deleterious effects on the general physical state of the animals.

II. The weights of the organs are presented in tabular form. The actual weights are given in table 1 and the relative weights, or the weights per kilogram of net body weight, in table 2. In both tables the order of organs and of animal groups is the same. For comparison, observations obtained from a series of 350 normal rabbits are given first. Then follow the results of this experiment in the order of light and dark room animals and inside and outside controls. With the exception of the outside controls, these major divisions are divided into five groups, comprising ten rabbits each, and corresponding to the two, four, six, eight and twelve week periods of exposure to the environments of the experiment. There were only four groups of outside controls. Finally, results are given for twenty normal rabbits examined on March 12, 1925, midway in time between the fourth and fifth experimental groups.

III. An analysis has been made of the organs weights of normal rabbits exposed to a constant illumination having none of the shorter ultraviolet rays and of other rabbits kept in darkness for periods of from two to twelve weeks.

The environment of constant illumination was associated with a well marked decrease in the relative weights of most organs, and in certain instances this occurred when the organs' weights of the controls were becoming increasingly large. There was also an associated effect of stabilization of organ weight.

The majority of the organs of rabbits caged in constant darkness also showed a tendency toward decreased and stabilized weights, but these effects were less pronounced than in the rabbits caged under conditions of constant illumination. A notable exception to this general result was the weight of the liver, which was markedly increased.

The results of this experiment support the conception that there is a relationship betwen light and the physical state of the animal organism which may be expressed in the concrete form implied by the tend or direction of organ weight.

AUTHOR'S SUMMARY.

AUTOPLASTIC THYMUS TRANSPLANTS: II. WITH PARTICULAR REFERENCE TO THE REGENERATION OF THE RETICULUM CELLS AND THE FORMATION OF HASSALL'S CORPUSCLES. HENRY L. JAFFE, J. Exper. Med. **44**:523, 1926.

Regeneration of a thymus transplant is characterized by hypertrophy and hyperplasia of the reticulum cells, leading to the formation of small and large atypical Hassall bodies during the early stages.

Regeneration is usually complete by the third week, when the newly formed lobules show differentiation into cortical and medullary zones, and typical Hassall bodies appear.

Typical Hassall corpuscles are also derived from the reticulum epithelial cells.

These corpuscles have no function, being aggregates of spent cells.

The thymus reticulum cells are actively phagocytic, and react rapidly when noxious influences are exerted on the gland.

AUTHOR'S SUMMARY.

EXPERIMENTAL GLOMERULONEPHRITIS INDUCED IN RABBITS WITH THE ENDOTOXIC PRINCIPLE OF STREPTOCOCCUS SCARLATINAE. CHARLES W. DUVAL and R. J. HIBBARD, J. Exper. Med. **44**:567, 1926.

Broth-grown cultures, cultures from blood agar slants and culture filtrates (Berkefeld N or V) of H. *Streptococcus scarlatinae* are without appreciable effect on the rabbit, no matter how large the dose or by what route introduced.

The active toxic principle of H. *Streptococcus scarlatinae* for rabbits is intimately associated with the protein of the bacterial cell, and is not given off in the artificial medium during the growth activity of the organism, indicating therefore, its endotoxic character.

The endotoxin is readily obtained from the viable scarlatinal cultures through the medium of the peritoneal cavity of the rabbit immunized against the homologous strain (Pfeiffer phenomenon). The toxic substance thus obtained we have termed a lysate.

The rabbit is highly susceptible to the in vivo prepared lysate of *Streptococcus scarlatinae*, at least from the cultures we have employed. The degree of the toxic effect on the rabbit depends on the size of the dose and the route through which it is introduced. The specific effects range from mild to severe and fatal forms of toxemia, as indicated by high fever, leukocytosis, paralysis and acute hemorrhagic glomerular nephritis.

The experimentally induced nephritic lesions are analogous in kind and variety to those of acute scarlatinal nephritis in man, including the "epithelial crescent" formation, hyaline thrombi of glomerular capillaries, hemorrhage into capsular space and necrosis of capillary tufts.

AUTHOR'S SUMMARY.

ANATOMY OF THE HEART IN TWO CASES OF SITUS TRANSVERSUS. HELEN B. TAUSSIG, Bull. Johns Hopkins Hosp. **39**:199, 1926.

The main gross anatomic structures and the deep muscle bundles of the ventricles presented the mirror image of the normal, while the direction of the superficial muscle bundles remained unchanged.

ARTERIOSCLEROSIS OF THE CEREBRAL VESSELS AND THE PATHOGENESIS OF HYPERTENSION. JAMES BORDLEY, III, and B. M. BAKER, JR., Bull. Johns Hopkins Hosp. **39**:229, 1926.

The explanation of hypertension may be found in the vascular changes in the brain stem.

A STUDY OF THE VARIATION IN NUMBER OF BLOOD CELLS OF NORMAL RABBITS. L. D. BUSHNELL and EDNA F. BANGS, J. Infect. Dis. **39**:291, 1926.

We may consider the figures obtained in this experiment as standards for the purpose of indicating conditions which affect the blood counts of normal rabbits.

In subsequent determinations on the blood of rabbits, variates whose values fall within the limits set by adding to, or subtracting from, the mean of the present series the probable error of the present series multiplied by 3.2, may be considered indicative of a normal condition of that blood.

Conversely, variates whose values fall without the limits just described may be considered as indicative of abnormal conditions of the blood.

The results of the work on the erythrocytes and leukocytes are of especial value, because counts of these two kinds of cells are very often used as a means

of diagnosis of pathologic or abnormal conditions which affect the blood. The determination of limits of normal variation serves as a criterion of those deviations from the mean necessary to indicate abnormal or pathologic conditions affecting the blood.

The probable errors obtained for the small lymphocytes and polymorphonuclear leukocytes can be applied to subsequent determinations, because there is less variation and less chance for error when a relatively high count is obtained. In normal bloods, small lymphocytes and polymorphonuclear leukocytes are always found, in varying quantities it is true, but are never entirely absent.

The same calculations may be applied to the modified Arneth's index determinations, as are applied to cell counts.

The probable error figures obtained for the large lymphocytes, large mononuclear leukocytes, eosinophils, basophiles and transition cells are of doubtful value. The fact that it is often impossible to find any of these types in a particular sample of blood makes it difficult to apply any limiting values, such as those described above.

AUTHOR'S SUMMARY.

A FURTHER NOTE ON HEPATO-LENTICULAR DEGENERATION. S. BARNES and E. W. HURST, Brain **49**:36, 1926.

The authors found marked degeneration in the frontal lobes, especially in the white matter. In one area a large cavity was found. There was less destruction in the lenticular nuclei. Marked increase in vascularity and the diffuse presence of large Alzheimer glia cells were described. The Kayser Fleischer zone of pigmentation in the cornea was considered as a hematogenous iron free pigment.

ROY GRINKER.

A CLINICAL AND PATHOLOGICAL RESUMÉ OF COMBINED DISEASES OF THE PYRAMIDAL AND EXTRAPYRAMIDAL SYSTEMS WITH SPECIAL REFERENCE TO A NEW SYNDROME. J. LHERMITTE and D. MCALPINE, Brain **49**:157, 1926.

In this combined syndrome the changes consisted of marked reduction of the cells of the putamen with neuroglial overgrowth. There was slight but definite reduction of the large striatal cells, with glial replacement. The ansa lenticularis was thinned and there was a degeneration of the pyramidal tract below the level of the medulla.

ROY GRINKER.

LYMPHORRHAGES IN THE MUSCLES IN EXOPHTHALMIC GOITER. L. S. DUDGEON and A. L. URQUHART, Brain **49**:182, 1926.

Lymphorrhages are described in the muscles of eight of nine patients, most marked in the ocular muscles. They are composed mainly of lymphocytes with a few plasma and endothelial cells and lie close to the blood vessels. They may be small or large, and atrophic changes or an interstitial myositis can be found in the adjacent muscle fibers.

ROY GRINKER.

ABSCESS OF THE SPINAL CORD. H. W. WOLTMAN and A. W. ADSON, Brain **49**: 193, 1926.

The authors report a case of a large spinal cord abscess with operation and practically complete recovery of all function. They find twenty-nine cases in the literature; all but one were fatal. They found eight secondary to diseases

of the spine, five from the lung, two from the urinary tract, two from trauma, one each from exposure, dermoid, meningocele, and endocarditis, and the remainder from unknown sources.

ROY GRINKER.

THE PROBLEM OF THE MONGOL. R. M. STEWART, Proc. Roy Soc. Med. (Section of Psychiatry) **19**:11, 1926.

In mongolian idiocy the author finds the skull bones thin, the nasal bones very small or failing, the brain small and light and the gyri few and wide. The insula may not be covered by the operculum. The endocrines are normal; abnormal pigmentation in the central nervous system and inflammation are not present. The pyramidal cells are decreased and show an embryonic character, the myelin sheaths are thin, the tangential cortical fibers decreased, and the Purkinje cells often have two nuclei. The author concludes that mongolism is not due to syphilis.

ROY GRINKER.

TUBERCULOSIS OF TISSUES OF MAMMALS IN CULTURE. ALEXANDRE A. MAXIMOW, Ann. d'anat path. **3**:1, 1926.

The genesis of the elements of which the tubercle in tuberculosis is made up is still unsettled. Of particular interest is the question concerning the origin of the epithelioid cells which are one of the characteristic elements of the tubercle. Conheim, Koch, Metchnikoff and others traced their origin to the hematogenous elements—leukocytes; Baumgarten, Orth and other Germans believed that they come exclusively from local fixed connective tissue elements. Recently, the opinion was to the effect that the epithelioid cell has a double origin: from the emigrated lymphocytes of the blood and from the fixed cells or polyblast, a conception advocated by Maximow since 1902.

The prevailing idea, however, is that the epithelioid cell, as well as the polyblast, originates from the local fixed connective tissue. Since the "fixed connective tissue," according to modern conception represents the fibroblast, vascular endothelium and the histiocytes (clasmatocytes), different authors have traced the origin of epithelioid cells now to the endothelium, now to the fibroblast, now to the polyblast.

The genesis of the lymphocytes, which are also a characteristic element of the tubercle, is also under discussion.

To trace the origin of all these cells, Maximow has recurred to an altogether new method: He tried to reproduce as much as possible, in vitro, the pathologic picture characteristic of the tuberculous process as seen in vivo. The advantages of the method of tissue cultures to study the correlation between the tubercle bacillus and the tissue cells is evident from the morphologic, as well as from other points of view. By using this method one eliminates the intervention of hematogenous elements; again, the tissue changes can be seen easily in the living state.

The lymphoid tissue of the mesenteric glands, the omentum and the loose intermuscular connective tissue of adult rabbits were used for the inoculation of two different strains of tubercle bacilli of human origin.

The author gives in great detail all the technic of his procedure. The first point of interest in this remarkable study is the fact that the growing tissue culture forms, with inoculated and proliferating tubercle bacilli, some kind of a symbiosis. Degeneration or death of the cultures occurs only in instances of contamination by some saprophytes. "The two elements," says the author,

"grow together for about three weeks." Ocasionally, isolated cells in perfect health, sometimes even in a state of division, may be seen surrounded by enormous masses of bacilli.

In the lymphoid tissue the most active elements are the reticular cells. They mobilize themselves, become hypertrophic, undergo division and transform themselves into large polyblasts, i. e., into epithelioid cells, which phagocytose actively tubercle bacilli.

The epithelioid cells gather in clumps corresponding to the tubercle, which could be designated "primitive tubercles." Numerous of these cells unite, apparently as a result of diminution of superficial tension of their cytoplasm, giving rise thus to the formation of giant cells of the Langhans type; the increase in the number of their nuclei is due to amitosis.

The lymphocytes, too, swell, and transform themselves into polyblasts, acquiring occasionally, as time goes on, an epithelioid character, and together with the reticular cells, they contribute to the formation of the tubercle and the giant cells. In their new form they become actively phagocytic.

Cells studded with tubercle bacilli preserve for a long time their vitality, being able to move and even to divide by karyokinesis. Maximow noted also in his cultures the final result seen in tuberculosis in vivo: caseation.

Analogous results are noted in cultures prepared from the mesentery and also from simple connective tissue.

The endothelium does not participate in the formation of the elements of the tubercle. (Maximow outlines that under "endothelium," he understands only the flat cells which line the blood vessels: capillaries, arteries, veins, the lymphatics and the heart.) These cells either preserve their tubular arrangement and form new capillaries or become transformed into fibroblasts. B. M. Fried.

New Studies of the Pathogenesis, Pathologic Anatomy, and Clinic of Tabes. G. R. Lafora, Encéphale **21**:161, 1926.

The author agrees with Richter and Schaffer that the primary lesion is a chronic inflammation of the pia and arachnoid with secondary involvement of the posterior roots.

Roy Grinker.

The Inflammatory Problem in the Central Nervous Syetem. D. J. MacPherson, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **27**:283, 1925.

In nonpoisoned animals, aseptic brain trauma produced a liberal connective tissue and glial reaction. In animals previously subjected to intravenous acid toxin, the connective tissue reaction predominated. Large degenerating ameboid glia cells were produced, but the glial reaction was minimal. Thyroidectomized animals reacted in the same way. The author believes that the action of acid substances is on the glia.

Roy Grinker.

Pathologic Anatomy and Pathology of the Cells of Leydig. Z. Morgenstern, J. medicobiol. **1**:29, 1925.

The cells of Leydig function in the interchange of lipoids between the blood and the spermatogenetic cells. They possess the property of reticulo-endothelial and macrophageal structures. Whether they furnish a storage place for lipoids of the spermatogenetic epithelium or act as an intermediary for transmission of lipoids, whether the hyperplastic foci indicate a forerunner of connective tissue organization, has thus far not been definitely determined.

S. Novakowsky.

PATHOLOGIC ANATOMIC CHANGES IN COMATOSE FORMS OF MALARIA. P. MOGUILNITSKY, J. medicobiol. **1**:54, 1926.

Most conspicuous of the many changes in the nervous system in comatose forms of malaria are those in the midbrain, peduncles, medula and the peripheral sympathetic nerves; those of the spinal cord, parasympathetic ganglions and nerves are less marked. Besides pigment and plasmodia, diffuse glia proliferation and formation of granulomas, multiple small hemorrhages, perivascular necrosis and destruction changes in the ganglion cells are recorded. In prolonged cases necrobiosis of the nerve tissue and connective tissue proliferation occur in the peripheral vegetative system. Polyganglioneuritis together with changes in the vegetative centers lead to varied symptoms of functional derangements of the heart, vascular system and gastro-intestinal tract, and to pigmentation. It should be noted that the connection between the striapallidum system and the midbrain is at present well established and the changes described explain the extrapyramidal and general vegetative symptoms and also suggest disorders in metabolism of protein, purin, fats, carbohydrates and inorganic compounds.

S. NOVAKOWSKY.

AUTOPSY METHODS FOR THE TOPOGRAPHIC REPRESENTATION OF PULMONARY CHANGES. L. BRAUER and T. FAHR, Beitr. z. Klin. d. Tuberk. **63**:659, 1926.

After discussing different methods advocated, the authors suggest as the most suitable one, injection of 75 per cent Jores solution plus 25 per cent formalin into the inferior vena cava. From 4 to 4½ liters are required. After one hour the entire thorax is removed, including its bony frame. The whole specimen is further hardened in the same fluid that is used for injection; after several weeks it is frozen and cut with an electric saw into horizontal slices of about 25 cm. thickness. The single sections are preserved in closed glass frames.

MAX PINNER.

ATYPICAL FORM OF TUBERCULOSIS. A. ESSER, Beitr. z. Klin. d. Tuberk. **63**:699; **64**:76, 1926.

The reported cases are atypical in the following respects: (1) propagation through the different organs; (2) tumor-like lesions, which are strictly productive with the formation of hyaline connective tissue; (3) acute tuberculous sepsis, and (4) isolated tuberculous lesions in spleen or liver, or trachea and bronchi without pulmonary foci. As to the anatomic character of the processes, four types may be distinguished: (1) almost purely caseous forms, predominant in frequency; (2) extremely productive forms, which are rare; (3) necrosing forms, which do not show caseation but coagulation necrosis, and (4) nonspecific necrosing forms, which appear as purulent lesions and which belong to the picture of the acute tuberculous sepsis.

MAX PINNER.

CONTRIBUTIONS TO THE PATHOLOGIC ANATOMY OF TUBERCULOSIS: I. BLOOD VESSELS IN TUBERCULOUS PULMONARY FOCI. II. A CONTRIBUTION TO THE GENESIS OF LANGHAN'S GIANT CELLS. H. WURM, Beitr. z. Klin. d. Tuberk. **63**:977, 1926.

In older productive foci which show already a peripheral encapsulation, one finds rather frequently capillaries, particularly in stages of acute exacerbation. This observation is significant for the explanation of endogenous reinfection and of tuberculous toxemia.

It was observed that capillaries in tuberculous pulmonary foci are frequently found in close relation to giant cells. Further studies led to the definite conclusion that giant cells may develop from capillary buds.

MAX PINNER.

HEMORRHAGIC INFARCTION OF THE NOSE. W. M. DE VRIES, Beitr. z. path. Anat. u. z. allg. Pathol. **75**:451, 1926.

In ten of some 8,300 necropsies comprising the material of the University of Amsterdam, hemorrhagic infarction of the tip of the nose was noted. All of these patients had died of decompensated heart lesions with passive congestion, and De Vries believes that the infarction of the nose was due to thrombosis of small vessels. Although he was unable to find any record of a similar condition in cardiac disease, he refers briefly to various other diseases in which a similar process has occasionally been described: typhus, diabetes and one case of aortic aneurysm. In all of these De Vries thinks that the underlying factor was thrombosis of the small vessels of the tip of the nose.

O. T. SCHULTZ.

CONGENITAL CYSTIC LIVER. MARGRIT TEUSCHER, Beitr. z. path. Anat. u. z. allg. Pathol. **75**:459, 1926.

Teuscher reports the occurrence of multiple cysts of the liver in two stillborn fetuses. In both, the kidneys were also cystic, and in one there were a few cysts in the pancreas. In one of the author's cases, the liver cysts were microscopic in size; in the other they could be seen with the naked eye. The cysts were situated in the periportal connective tissue and they were lined by a complete single layer of bile-duct epithelium. Serial sections proved that the cysts occurred in the course of interlobular bile ducts, in none of which could any area of occlusion be found. The small cysts in the pancreas also occurred in the interlobular ducts, which were not occluded. Because of her observations, Teuscher could not accept for her cases the mechanism proposed by von Meyenburg, namely, the development of the duct and parenchymatous portions of the liver from separate anlagen, cyst formation being due to the failure of union of the ducts of the parenchymatous portion with those entering the liver from the hilum, a mechanism which homologizes congenital cystic liver with congenital cystic kidney. Teuscher concludes that congenital cystic liver is the result of a developmental anomaly associated with greater proliferative activity on the part of both the epithelium of the interlobular bile ducts and of the periportal connective tissue. This anomaly involves more especially the embryonic plexus-like hepatic ducts at the hilum described by Hertwig, Lewis and Aron. An inhibitory process (Hemmung) also plays a part, in that some of the small embryonic periportal and intralobular ducts do not undergo the normal regression, and disappearance and may become cystic because of the proliferative activity of the epithelium.

O. T. SCHULTZ.

NUCLEAR DERIVATIVES IN THE LAMINATED CATARACT OF DOGS. WESTHUES, Beitr. z. path. u. z. allg. Pathol. **75**:603, 1926.

By means of the nuclear reaction, Westhues established the nuclear origin of stainable bodies which he had previously described in the laminated cataract of dogs. Similar bodies of nuclear origin do not occur in the traumatic or senile cataract of dogs.

O. T. SCHULTZ.

EXPERIMENTAL OBSERVATIONS ON THE OCCURRENCE OF FATTY DEGENERATION OF THE LIVER. ORONZIO MACCHIARULO, Frankfurt Ztschr. f. Path. **34**:37, 1926.

The author produced fatty degeneration of the liver in rabbits by combined chloroform injections and cholesterol feeding. A 10 per cent solution of chloroform in olive oil was injected subcutaneously, followed by the administration of a 20 per cent solution of cholesterol in sunflower or olive oil by stomach tube. By this method the author was able to produce isotropic and anisotropic fatty degeneration of the liver cells and Kupffer cells with a heavy accumulation of lipoid-laden phagocytes in the connective tissue. The cirrhotic changes in the spherical and ringshaped secondary hemorrhages.

E. M. HALL.

VASCULAR TUBERCULOSIS OF THE PIA-ARACHNOID WITH FATAL INTRACEREBRAL HEMORRHAGE. MARIA KAUP, Frankfurt. Ztschr. f. Path. **34**:116, 1926.

The author studied grossly and microscopically a case of tuberculosis of the pia-arachnoid in which severe hemorrhage had occurred in the substance of the brain. She found in this case, peculiar changes in the pial vessels, confined almost exclusively to the veins, wherein the walls over wide stretches were altered by the production of tuberculous granulation tissue. The growth of this new tissue had led to narrowing or complete obliteration of the vessel associated with caseation and thrombus formation. These changes had produced a high grade venous stasis of the proximal portions of the veins, with the development of varices where stasis was greatest. Nutritional changes in the walls of veins and surrounding brain substance, followed, leading to degenerative changes in the vessels, edema and atrophy of the brain. Actual hemorrhage apparently had been precipitated by the sudden thrombotic obstruction of an intergyral vein by which the circulatory congestion was intensified. The bleeding had occurred chiefly by diapedesis, with the formation of typical liver were more marked than when chloroform was used alone.

E. M. HALL.

THE NEUROGLIA AND THE THIRD ELEMENT OF THE CENTRAL NERVOUS SYSTEM. P. DEL RIO HORTEGO, Neurol, Zentralbl. **44**:139, 1926.

By means of his specific stains the author is able to differentiate the various types of neuroglia. He finds that the true glia may be classified into the astrocytes or fibrous glia, the cytoplasmic glia, and the oligodendroglia or satellites or interfascicular glia. The third element in the nervous system has heretofore been also considered as glia and called rod cells or microglia. Hortego shows that these are of mesodermic origin and terms them mesoglia. As a result of Penfield's and the author's experiments it can be shown that it is these mesoglia which become free and rounded and are the active phagocytes within the nervous system. Transitions from mesoglia to gitter cells have been described. This and other contributions from the Spanish school are revising the entire conception of brain repair.

ROY GRINKER.

EFFECT OF ROENTGEN RAYS ON THE CENTRAL NERVOUS SYSTEM. A. RACHMANOW, Strahlentherapie **23**:318, 1926.

In order to study the local effect of roentgen rays on the central nervous system, the author used vital staining. White mice received hypodermic injections of 1.5 cc. of 1 per cent trypan blue solution, every five to seven days, receiving a total of from 2.5 to 3.5 cc.; part of the dye was injected before, the rest after the exposure. A thorough study of the untreated animals that had received injec-

tions furnished the necessary data for comparison. Unfiltered radiation (quality Bauer 9) at 23 cm. distance was used; a dose of 3 according to the Sabourand and Noiré scale of roentgen-ray dosage, which corresponded to from twelve to eighteen minutes' exposure; the rays reached the head only, the rest of the body being carefully protected by lead rubber. On the sixth day after treatment, a severe conjunctivitis appeared; after two weeks, epilation and sometimes erosion occurred; a few mice died; the majority were killed with ether between the fourth and sixth day. The brain, spinal cord and inner organs were taken out and fixed in 10 per cent formol, and frozen sections were stained with cochineal or alum-carmine. As the principal change after irradiation, an increase of vitally stained histiocytes and the appearance of blue stained drops in the endothelium of the blood vessels were noticed. The spinal cord presented the same changes but to a lesser degree. By irradiating the body and covering the brain carefully, the changes described could not be reproduced. It is evident, therefore, that the effect observed was due to the direct exposure of the nervous system.

E. A. POHLE.

LAMINAR CORTICAL SOFTENING FROM ARTERIOSCLEROSIS OF THE SMALL CORTICAL VESSELS. F. BRINKMANN, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:182, 1926.

The author describes two cases of extensive softening of an individual cortical layer.

ROY GRINKER.

COLLOID DEGENERATION AND COAGULATION NECROSIS IN THE BRAIN. E. STRÄUSSLER and G. KOSKINAS, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:344, 1926.

A case of general paralysis with marked hyalin degeneration was studied. The process began with a thickening of the reticulum into which was deposited a granular substance. The vessels were hyalinized. The ganglion cells degenerated and there was a proliferation of large protoplasmic glia cells and gliogenous giant cells.

ROY GRINKER.

PATHOLOGIC ANATOMY OF SUBARACHNOID HEMORRHAGE. G. S. MARGOLIN, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:616, 1926.

A case of subarachnoid hemorrhage revealed arteriosclerosis of the pial vessels.

ROY GRINKER.

MICROSCOPIC CHANGES OF GENERAL PARALYSIS. L. BOUMAN, Ztschr. f. d. ges. Neurol. u. Psychiat. **101**:68, 1926.

A case of clinically severe general paralysis with a strongly positive Wassermann reaction under malaria treatment revealed no psychiatric change but an almost completely negative Wassermann reaction. The brain contained a marked but quiescent parenchymatous change and a most unusually mild infiltration with but few lymphocytes.

ROY GRINKER.

THE CLINICAL AND HISTOPATHOLOGIC ASPECT OF THE PSYCHOSES OF TABES. A. JAKOB, Ztschr. f. d. ges. Neurol. u. psychiat. **101**:227, 1926.

In the psychoses of tabes there is a pathologic basis which is unspecific and resembles any toxic process. There are mild diffuse parenchymatous changes and changes in the vessel walls.

ROY GRINKER.

PATHOLOGY AND PATHOGENESIS OF BRAIN SYPHILIS AND GENERAL PARALYSIS. H. SPATZ, Ztschr. f. d. ges. Neurol. u. Psychiat. **101**:644, 1926.

Tabes, general paralysis and cerebral syphilis should not be classified together. In cerebrospinal syphilis the inflammation is on the surface of the brain, in the meninges and on the ventricular surfaces. In general paralysis the inflammation is deeper in the basal ganglia and deep cortical layers. Spatz concludes that cerebrospinal syphilis is spread by means of the spinal fluid while general paralysis is of hematogenous origin.

ROY GRINKER.

THE ANATOMIC OBSERVATIONS IN A PATIENT WITH HUNTINGTON'S CHOREA HAVING WILSON'S SYNDROME. W. SPIELMEYER, Ztschr. f. d. ges. Neurol. u. Psychiat. **101**:701, 1926.

A case clinically resembling Wilson's disease revealed the typical pathologic condition of Huntington's chorea. The caudate, putamen and pallidal nuclei were grossly shrunken. The brain was small and the liver normal. There was a pure degeneration of the small striatal cells and some large cells were affected. Status fibrosus was noted in the putamen and there was a relative vessel increase. The pallidum was atrophic, and the red zone of the substantia nigra was degenerated.

ROY GRINKER.

THE NEUROHISTOPATHOLOGY OF PELLAGRA. N. W. WINKELMAN, Ztschr. f. d. ges. Neurol. u. Psychiat. **102**:38, 1926.

The author has studied three cases of pellagra with the following observations: (1) hyaline vascular degeneration of the small vessels of the pia and the central structures; (2) diffuse fatty changes in the parenchyma, especially in the ganglion cells, particularly in the layers 3 and 5; (3) primary irritative changes in the large motor ganglion cells of the motor cortex.

The changes were purely degenerative without any correlation between the severity of the symptoms and the parenchymatous degeneration.

ROY GRINKER.

A CASE OF PUERPERAL CHOREA OF FIVE MONTHS' DURATION. N. W. WINKELMAN, Ztschr. f. d. ges. Neurol. u. Psychiat. **102**:56, 1926.

The microscopic changes in this case consisted of proliferation of the walls of the smaller vessels in all parts of the brain. There was swelling of the endothelial lining of the larger vessels. Parenchymatous changes were most severe in the caudate nuclei and consisted of severe degeneration of the small ganglion cells, diffuse glia cell proliferation and perivascular edema.

ROY GRINKER.

CONCERNING THE FINDING OF MILIARY GUMMAS IN GENERAL PARALYSIS. A. JAKOB, Ztschr. f. d. ges. Neurol. u. Psychiat. **102**:313, 1926.

The author reiterates his belief, in spite of much adverse criticism by Spielmeyer, that in many cases of severe galloping general paralysis, especially those associated with epileptiform attacks, miliary gummas are found frequently. Jakob believes that this is the last attempt by the host at combating the spirochete.

ROY GRINKER.

AIR EMBOLISM IN CESAREAN SECTION. L. KRAUL, Zentralbl. f. Gynäk. **50**:1956, 1926.

In a twenty year old primipara having a flat rachitic pelvis, with a conjugata vera of 7 cm. and a baby weighing 3,250 Gm., on whom a transperitoneal cesarean section was done seven hours after the onset of labor, death from air embolism occurred twenty minutes after the beginning of the operation. Cyanosis set in shortly after the uterus had been sutured and squeezed to expel retained blood. At the autopsy air was found in the ovarian and renal veins, inferior vena cava and right auricle, and it was estimated that about 150 cc. of air escaped from the latter when it was opened under water. The placental site was on the fundus and dorsal wall and therefore drained into the spermatic plexus which empties into the left renal vein or into the inferior vena cava high up where it comes into the aspiratory influence of the diaphragm.

GEORGE RUKSTINAT.

Pathologic Chemistry

THE QUANTITIES OF SERUM ALBUMIN, GLOBULIN AND FIBRINOGEN IN THE BLOOD PLASMA IN ACUTE AND CHRONIC NEPHROPATHIES. G. FAHR and W. W. SWANSON, Arch. Int. Med. **38**:510, 1926.

In glomerulonephritis there is a tendency to a reduction in the total protein content of the plasma. This reduction is due largely to decrease in serum albumin content. Serum globulin content may rise slightly at the same time that serum albumin falls. The reduction in protein content of the plasma is usually correlated with marked loss of protein in the urine, and is probably due largely to loss in the urine. High protein (200 Gm. per day) feeding may not cause the protein content in the blood to rise more than very slowly. Although reduction in protein content, especially in serum albumin content of the plasma, is frequently associated with marked edema, and although marked edema is frequently associated with low protein content of the plasma, yet low protein content is not in any sense a prominent factor in producing the edema, for cases of nephritis may develop edema before the protein content of the plasma has fallen below the normal range, and with reduced total and markedly reduced serum albumin content of the plasma abundant diuresis may be going on. In order to evaluate the significance of the osmotic pressure of the colloids for edema formation in nephritis, it will be necessary to study the relation of this pressure measured directly during the course of edema formation and the disappearance and under experimental control.

S. A. LEVINSON.

THE CHEMICAL NATURE OF SUBSTANCES REQUIRED FOR CELL MULTIPLICATION. ALEXIS CARREL and LILLIAN E. BAKER, J. Exper. Med. **44**:503, 1926.

Fibroblasts and epithelial cells in pure culture obtain the nitrogen, which they build into protoplasm, from proteoses and possibly other primary derivatives of proteins. These proteoses have been prepared from embryo tissues, egg white, commercial fibrin, rabbit brain, Witte's peptone, etc.

The presence in embryo juice of a hormone that stimulates cell division is improbable.

Proteoses separated from peptic digests of fibrin by sodium sulphate determine a more abundant and prolonged multiplication of the fibroblasts than is produced by embryo juice. Peptones and the smaller split products appear to furnish some nutrient material, but do not cause the rapid proliferation characteristic of proteoses, and are sometimes toxic for tissue cells.

Possibly the effect of embryo juice on fibroblasts and epithelium is due to the splitting of the protein of the juice into proteoses by the cell enzymes, or by other enzymes activated by the presence of living cells. AUTHOR'S SUMMARY.

EXPERIMENTAL AMYLOIDOSIS. E. LETTERER, Beitr. z. path. Anat. u. z. allg. Pathol. **75**:486, 1926.

In an article of 102 pages with 153 bibliographic references, Letterer describes in detail his own experimental researches on the production of amyloidosis in mice and discusses the pathogenesis of the process. Although amyloid deposition as a rule, but not invariably, follows the repeated injection of nutrose or casein into mice, other parenterally introduced proteins were found by Letterer also to have the same effect. In one half of the series of animals in which the experiment was tried, the intraperitoneal implantation of species homologous organs led to amyloidosis. Injection of colloidal sulphur and colloidal selenium had a similar effect; colloidal iron, however, was found to be inactive in the production of amyloid. The various materials which may cause amyloidosis are substances which stimulate the cells of the tissue to the formation from their own cytoplasm of materials which circulate in the blood plasma as globulins. Letterer believes that globulin is the mother substance of amyloid and that the increased transfer of globulin from the cells to the tissue fluids, as the result of the parenteral introduction of a variety of substances, leads to the deposition of colloid outside the blood vessels in those animals in which an altered colloid chemical mechanism interferes with the entrance of the globulin into the blood.

O. T. SCHULTZ.

STUDIES ON SERUM PROTEASES. PART 10. ON THE NUMBER OF SERUM PROTEASES, WITH REFERENCE TO THE DIFFERENTIATION AND CHARACTERIZATION OF THE DIFFERENT KINDS. S. KIMURA, Tohoku J. Exper. Med. **7**:560, 1926.

In human serum three proteases are differentiated by their optimum activities at different hydrogen ion concentrations: serum pepsin at p_H 1.5 to 1.9; serum autolytic ferment at from 3.9 to 4.4, and serum tryptase at from 6.9 to 8.4. The action of each is like that of the corresponding ferment in the digestive tract: pepsin forms peptones, and tryptase splits true protein to amino acids. Ereptase could not be distinguished from tryptase by the optimum p_H method. All ferments are weakened by heat at 55 C. for thirty minutes and destroyed at 60 C. Pepsin and tryptase, but not the autolytic ferment, are increasingly active in water dilutions. Within wide limits corresponding proteases can also be distinguished in the serums of the horse, beef, the pig and the dog. E. B. PERRY.

Microbiology and Parasitology

GLANDULAR FEVER (INFECTIOUS MONONUCLEOSIS). C. W. BALDRIDGE, F. J. ROHNER and G. H. HANSMANN, Arch. Int. Med. **38**:413, 1926.

Glandular fever (infectious mononucleosis) is an acute infectious disease of unknown etiology, usually of short duration, characterized by fever, enlarged lymph glands and the occurrence of numerous abnormal mononuclear cells in the circulating blood. Streptococci, diptheroid bacilli and the spirochetes and fusiform bacillus of Vincent's angina have been mentioned as etiologic agents. The portal of entry is considered by some to be the faucial or pharyngeal tonsils, by others the gum margins and by still others the gastro-intestinal tract.

Neither the organism causing the disease nor its portal of entry has been proved. Several well defined epidemics have been reported from various countries in the temperate zones. The symptomatology is similar to that of other acute infectious diseases, with the additional symptoms caused by enlarged tender glands, either superficial or between the muscle layers of the neck. The physical conditions are confined largely to the fixed lymphatic tissue. The modes of onset, because of their great variability, embody one of the chief difficulties in diagnosis. The total leukocyte counts are usually above normal at the onset and below normal during convalescence. A polymorphonuclear leukocytosis may occur at the onset, especially in cases with marked febrile reactions. Some time during the course the blood shows a rather marked increase in abnormal mononuclear cells. Many of these abnormal cells are lymphoid in nature but some are no doubt endothelial leukocytes or monocytes. Occasionally the monocytes may outnumber the lymphoid cells. There often is an almost complete lack of normal small lymphocytes in the blood stream. The occurrence of a relative or absolute lymphocytosis with abnormal lymphoid cells in the blood stream is significant only of acute lymphoid hyperplasia and is no way limited to, nor specific for, glandular fever; nor does the percentage of these abnormal cells bear any direct relation to the amount of demonstrable glandular enlargement. The diagnosis of glandular fever is often difficult because a specific test does not exist; the disease may so closely resemble other acute infections, because of its bizarre manifestations and because so many very mild cases are encountered.

S. A. Levinson.

Aid in the Diagnosis of Typhoid Fever. C. A. Mills and K. V. Kitzmiller, Arch. Int. Med. **38**:544, 1926.

The results of tests on thirteen typhoid patients demonstrate a high antithrombin production during the febrile period, with practically twice the normal antithrombin content in every case. All but two of the nontyphoid cases that showed this high antithrombin production were afebrile cases of a distinctly chronic character, so that confusion in diagnosis was not possible. One of the two exceptions was the case of a boy with high fever, negative physical characteristics and high leukocytosis, who two days later developed typical lobar pneumonia. The leukocytosis here would have practically ruled out typhoid fever. The other exception was the case of a young girl whose fever lasted only two days, and in whose case diagnosis was not made before discharge from the hospital. Miliary tuberculosis, so often confused with typhoid fever, is entirely different in its antithrombin curve. Here, instead of a great excess of antithrombin, there is actually less than normal. A logical basis is established for explaining the hemorrhagic tendency in typhoid fever.

S. A. Levinson.

Studies on the Biology of Streptococcus: VI. Biology of Hemolytic Streptococcus: Antigenic Relationships Between Strains of the Scarlatinal and Erysipelas Groups. Franklin A. Stevens and A. R. Dochez, J. Exper. Med. **44**:439, 1926.

Agglutination and absorption tests were made with three erysipelas streptococcus immune serums and several strains of erysipelas and scarlatinal streptococci. Each serum was tested for agglutinins in a 1:20 dilution with fractions and multiples of a previously determined absorptive dose of bacteria of the homologous strain, then absorbed, first with the homologous strain and then in turn with each of the strains corresponding to the two other serums, and after

each absorption tested for residual agglutinins with the various erysipelas and scarlatinal strains. The results indicated that strain specificity dominated group specificity, and scarlatinal and erysipelas strains could not be distinguished by this method. A discussion of the probable presence in each strain of many antigenic fractions concludes that the "reactions in the absorbed serum would depend on the qualitative and quantitative relationships between the component fractions in the serum, the absorbing strain and the strain agglutinated," and that knowledge concerning the specificity and relationship of such antigenic fractions must come from study of chemically refined preparations.

E. B. PERRY.

ETIOLOGY OF OROYA FEVER: II. VIABILITY OF BARTONELLA BACILLIFORMIS IN CULTURES AND IN THE PRESERVED BLOOD AND AN EXCISED NODULE OF MACACUS RHESUS. HYDEYO NOGUCHI, J. Exper. Med. **44**:533, 1926.

Cultural tests showed that *Bartonella bacilliformis* in citrated blood from infected monkeys was viable after 152 days at 4 C., and had increased in numbers after sixty-seven days at room temperature; in an excised nodule from a monkey it survived for at least fifty-six days at 4 C., or for twenty-eight days at room temperature; and in cultures on leptospira medium it was transferable after 120 days at 25 C., and after twenty-eight days at 25 C., followed by four months in the refrigerator, but died after fifty days at 37 C. The conclusion was drawn that cultural studies of pathologic material from distant parts of the world might be fruitful, even if many days or weeks intervene.

E. B. PERRY.

THE RELATION OF BACTERIUM PNEUMOSINTES TO INFLUENZA: A STUDY WITH A STRAIN OF THE ORGANISM DERIVED FROM THE NASOPHARYPGEAL WASHINGS OF A CASE OF INFLUENZA. MILTON W. HALL, J. Exper. Med. **44**:539, 1926.

Nasopharyngeal washings from a case of epidemic influenza have proved capable of initiating a pathologic change in rabbits and in guinea-pigs characterized after an incubation period of one or two days by some elevation of temperature, reduction in the number of circulating leukocytes, especially of the mononuclears, and a pulmonary lesion during the period of reaction, which is distinguishable from those accidentally incurred at the time of death.

From one such animal, in the second passage of the virus, an anaerobic coccobacillus, corresponding in all respects to *Bacterium pneumosintes,* was isolated by the method employed by Olitsky and Gates.

This organism also proved capable of initiating the pathologic change found in animals after inoculation with influenzal material.

The observation of Olitsky and Gates that the presence of this organism in the lungs of experimental animals predisposes to pulmonary localization of other bacteria with the production of definite pneumonic lesions has been confirmed.

Bacterium pneumonsintes infections may be induced by the subcutaneous injection of infected material.

AUTHOR'S SUMMARY.

PHYSIOLOGIC ACTION OF CERTAIN CULTURES OF THE GAS BACILLUS. ARTHUR ISAAC KENDALL and FRANCIS OTTO SCHMITT, J. Infect. Dis. **39**:250, 1926.

A histamine-like substance has been described, occurring in a majority of the seventy-two strains of the gas bacillus thus far studied.

This substance induces histamine-like contractures both in the isolated uterus and in the isolated small intestine of the guinea-pig.

A theory of the chemical formation of this substance is proffered.

The theoretical relationship of the substance to certain clinical cases is discussed.

AUTHORS' SUMMARY.

THE BIOLOGY OF OÏDIUM ALBICANS, WITH SPECIAL REFERENCE TO MYCELIAL PRODUCTION. A. A. DRAPER, J. Infect. Dis. **39**:261, 1926.

Yeasts of *Oïdium albicans*, when grown in carrot infusion, developed as mycelia below a certain level in the test tube. The ash of carrots contained some substance that influenced such mycelial growth. Analyses of the ash showed that it contained a large amount of phosphorus.

Various phosphate containing salts, in appropriate concentrations in 1 per cent peptone solutions, supported the hyphae growth.

The organisms grew as mycelia in meat infusion agar if a small amount of inorganic phosphate or carrot infusion was added, and special partial tension conditions were maintained.

Various strains of the organism differed in their biochemical and physiologic activities. Cells of the same strain when grown in different phosphate mediums developed type colonies that were specific for their respective mediums. Three such types were observed.

A type grown in its specific medium over a considerable period of time did not retain its type characters when transplanted into a medium specific for another type.

Exposure of cells from a given type colony to an appropriate amount of heat tended to fix the type colony characters to the extent that they were retained when they were seeded in a medium which usually supported another type. By this method type 1 was fixed on iron phosphate ($Fe\ PO_4 \cdot 4H_2O$) medium, and type 2 was partially fixed on carrot infusion medium. The degree of permanence of this fixation has not yet been determined.

AUTHOR'S SUMMARY.

THE INTERVENOUS USE OF ACRIVIOLET AND OF MERCUROCHROME IN BACTERIAL INFECTIONS. JAMES S. SIMMONS, J. Infect. Dis. **39**:273, 1926.

Both acriviolet and mercurochrome-220 soluble dissolved in water or salt solution, are effective bactericidal agents in vitro.

Both dyes in 5 per cent solution in 50 per cent alcohol were found to be fairly good skin disinfectants against the normal organisms of the skin and throat.

The presence of blood reduced the in vitro bactericidal action of both dyes against staphylococci, and the presence of ox bile had the same effect in regard to the typhoid bacilli. To obtain effective concentrations in the body would have required the intravenous injection of lethal doses of the dyes.

Acriviolet had a toxic action on normal tissues: (*a*) injected subcutaneously it resulted in a marked necrosis of the skin, while (*b*) intravenously, it caused liver and kidney injury varying in degree with the dose. Single doses of from 5 to 8 mg. per kilogram were followed by functional disturbances; 9 mg. per kilogram or more, by degenerative lesions which were histologically demonstrable, and 20 mg. or larger doses, by death.

Acriviolet, when used intravenously in the treatment of staphylococcus septicemia in rabbits, did not kill the organisms, or prevent the formation of typical

staphylococcic lesions. It did hasten the death of overwhelmingly infected animals, and it caused the death of animals infected with nonlethal amounts of staphylococci.

Acriviolet, when used intravenously in the treatment of eight patients, including six with septicemia, did not prove to be of value. Two patients were improved after treatment, but in one the focus of infection had been drained, while the other was already well on the road to spontaneous recovery, when treatment was begun. The condition of two patients was unchanged by the dye, while four became much worse and three of these died.

Intravenously, even in doses of 3 and 5 mg. per kilogram of body weight, mercurochrome-220 soluble produced symptoms of mercurial poisoning.

Ten patients with genito-urinary infections were given mercurochrome-220 soluble intravenously without beneficial results; and in one with septicemia due to *Streptococcus hemolyticus* the organisms became more numerous in the blood stream after treatment, and the patient died.

Mercurochrome-220 soluble injected intravenously into rabbits, immediately after infection with staphylococci, did not kill the infecting organisms or prevent the formation of typical staphylococcic lesions.

Mercurochrome-220 soluble given intravenously or by mouth failed to kill typhoid bacilli in the gallbladder of animals suffering with typhoid cholecystitis.

In view of the work here reported, it is not believed that the intravenous use of either mercurochrome-220 soluble or acriviolet offers promise of beneficial results in the treatment of bacterial infections.

AUTHOR'S SUMMARY.

HEAT RESISTANCE STUDIES: 2. THE PROTECTIVE EFFECT OF SODIUM CHLORIDE ON BACTERIAL SPORES HEATED IN PEA LIQUOR. J. A. VILJOEN, J. Infect. Dis. **39**:286, 1926.

It has been shown that salt protects spores heated in pea liquor. The protective effect is observed with concentration up to 4 per cent. The increase of time necessary to kill the spore in the presence of salt is considerable in some cases. The resistance of all the individual spores in the suspension is increased. Under the influence of heat the spores decrease according to the law of unimolecular chemical reaction.

AUTHOR'S SUMMARY.

A METHOD FOR THE DETECTION OF CHANGES IN GELATIN DUE TO BACTERIA. WILLIAM C. FRAZIER, J. Infect. Dis. **39**:302, 1926.

The gelatin-agar plate method for the detection of a change in the composition of gelatin due to bacteria has been described. A nutrient agar is prepared with gelatin as the chief source of nitrogen. Duplicate plates of hardened gelatin-agar are so inoculated as to form giant colonies, and incubated for several days. When a plate is flooded with acid bichloride of mercury solution, a change in the gelatin due to bacteria is indicated by a clear zone about the giant colony, surrounded by precipitated gelatin. In a duplicate plate, flooded with tannic acid solution, a change is indicated by a precipitate about the colony, or with more strongly proteolytic organisms by a clear zone surrounded by a white precipitate in the form of a ring.

By the "amino-p_H" method which has been described, an increase in amino nitrogen in a gelatin solution can be detected.

Organisms may be placed in definite groups on the basis of their action on gelatin by use of the gelatin-agar plate method and the "amino-p_H" method.

AUTHOR'S SUMMARY.

A NEW METHOD FOR SUSPENDING AND COUNTING LIVING TUBERCLE BACILLI. FREDERIC B. JENNINGS, JR., J. Infect. Dis. **39**:310, 1926.

In this paper is presented an accurate method for suspending and counting living tubercle bacilli. The importance of such a method lies in the fact that a precise study of experimental tuberculosis can now be undertaken, with the assurance that the infecting doses, given to smaller laboratory animals, will be uniform. In the past, the methods for determining and controlling these doses have been inadequate, and consequently experiments in tuberculosis immunity were hampered.

AUTHOR'S SUMMARY.

SPONTANEOUS TUBERCULOSIS IN SALT WATER FISH. JOSEPH D. ARONSON, J. Infect. Dis. **39**:315, 1926.

Tubercles were found in various organs of salt water fish found dead in the tanks of the Philadelphia Aquarium, and acid-fast bacilli occurred within them.

Nodules found in the liver resembled, in some respects, the tubercles of mammals, and masses of acidfast bacilli were found in these nodules. In the spleen, mycotic emboli were found in the blood vessels, and necrosis of vessel walls and of splenic tissue occurred.

From these lesions was isolated an acid-fast, chromogenic, pleomorphic bacillus which grows best at from 18 to 20 C., is pathogenic for pigeons, mice, gold fish and frogs but does not kill rabbits or guinea-pigs.

The cultures isolated from these salt water fish differ in antigenic characters from the avian and mammalian varieties of *Bacillus tuberculosis*, from acid-fast bacilli isolated from poikilothermic animals and from saprophytic acid-fast bacilli.

The name *Mycobacterium marium* is suggested for this organism.

AUTHOR'S SUMMARY.

A HIGHLY HEAT-RESISTANT SPORULATING ANAEROBIC BACTERIUM: CLOSTRIDIUM CALORITOLERANS, N. SP. K. F. MEYER and O. W. LANG, J. Infect. Dis. **39**:321, 1926.

This report describes the morphology, the cultural, the physiologic and the serologic reactions, and the heat resistance of a terminally spored anaerobic bacterium for which the specific name "*Clostridium caloritolerans*, N. Sp." is herewith proposed.

AUTHORS' SUMMARY.

CHARACTERISTICS OF A NEW TYPE STRAIN OF CL. TETANI. GEORGE E. COLEMAN and K. F. MEYER, J. Infect. Dis. **39**:328, 1926.

A strain of *Clostridium tetani* tentatively considered as type 8 has been studied comparatively with three type 1 strains. Marked differences other than serologic have not been noted between these strains.

AUTHORS' SUMMARY.

PROPHYLAXIS AND TREATMENT OF SNUFFLES. ASAZO TANAKA, J. Infect. Dis. **39**:337, 1926.

Rabbits which receive injections with *Bacterium lepisepticum* or *Bacillus bronchisepticus* develop agglutinins for the homologous organisms.

B. bronchisepticus vaccination gives slight but definite protection against infection with *B. bronchisepticus* but not against *Bact. lepisepticum. Bact. lepisepticum* vaccination gives a little protection against infection with *Bact. lepisepticum.*

B. bronchisepticus immune serum possesses some protective power against the toxic action of this organism on the leukocytes. The immune serum of *Bact. lepisepticum* has little protective power against the toxic action of the organism on the leukocytes.

Animals were not protected against snuffles by repeated injections of these organisms. These observations do not agree with those of Ferry and Hoskins (J. Lab. & Clin. Med. **5**:311, 1919) who report: "The disease can in a large measure be controlled with a vaccine . . . . of *B. bronchisepticus, Bact. lepisepticum* and *Staphylococcus albus.*"

Rabbits which have recovered from snuffles, or have improved after severe infections (of the *Bact. lepisepticum* type), or have had subcutaneous abscesses, seem to possess very little, if any, resistance to subsequent snuffles infection.

Treatment with germicidal dyes, either intravenously or intranasally, has no effect in severe cases of snuffles, because the sinuses are severely affected.

Repeated inhalation of chlorine gas seems to have little influence on the course of symptoms in rabbits with snuffles, causing, perhaps, a temporary improvement, but never curing the condition.

AUTHOR'S SUMMARY.

THE PURIFICATION OF BOTULINUM TOXIN XXVII. E. WAGNER SOMMER, H. SOMMER and K. F. MEYER, J. Infect. Dis. **39**:345, 1926.

Isolation of botulinum toxin has been attempted by selective adsorption on colloidal aluminum hydroxide, elution with secondary ammonium phosphate, dialysis and evaporation at 40 C. Dried toxins with titers of from 0.2 to 4.0 microgram (μ) per minimum lethal dose for the mouse have been obtained. All preparations give slight protein and ferment reactions. Precipitation with ammonium sulphate has yielded a toxin with similar properties.

AUTHORS' SUMMARY.

SELECTIVE MEDIUMS IN THE DIAGNOSIS OF RODENT PLAGUE. PLAGUE STUDIES 1. K. F. MEYER and A. P. BATCHELDER, J. Infect. Dis. **39**:370, 1926.

An autoclaved hormone beef heart, or veal Berna peptone agar prepared according to the formula of Huntoon is rendered most suitable for the cultivation of *Pasteurella pestis* by the addition of 0.025 per cent (0.25 cc. of a freshly prepared 10 per cent solution) sodium sulphite and 1/400 per cent (2.5 cc. of a 1:1,000 solution per hundred cubic centimeters) of gentian violet (improved Coleman Bell). Such a medium inhibits the most troublesome contaminators usually encountered in diagnostic work on rats and squirrels. The large colonies, which develop in from thirty-six to forty-eight hours, are characteristic and may be identified by slide agglutination tests. The advantages of a gentian violet enrichment broth for the detection of plague without lesions are discussed.

AUTHORS' SUMMARY.

A Disease in Wild Rats Caused by Pasteurella Muricida, N. Sp. Plague Studies 2. K. F. Meyer and A. P. Batchelder, J. Infect. Dis. **39**:386, 1926.

A detailed pathologic, anatomic and bacteriologic study of eighty-eight wild rats caught in the course of plague control work in Oakland and Alameda, California, proved the existence of four rodent diseases, hemorrhagic septicemia (pasteurella), plagus, rat typhoid (due to *Bacillus enteritidis* and *Bacillus paratyphosus B*) and pseudotuberculosis (due to *Bacillus pseudotuberculosis rodentium* Pfeiffer). The comparative anatomic observations and the significance of the diagnostic guinea-pig inoculations and cultures are discussed.

The causative organism of the hemorrhagic septicemia for which a new species name, *Pasteurella muricida* (N. Sp.) is proposed, resembles morphologically, culturally, biochemically and serologically the well known representatives of the pasteurella group. It is highly pathogenic for guinea-pigs, rabbits, mice, and white and gray rats. Barnyard birds and cats are refractory. A spontaneous epidemic among laboratory rats introduced by an animal experimentally infected by the nasal route is reported.

Authors' Summary.

Incidence and Therapeutic Value of Staphylococcus Bacteriophage in Antrum Infections. Elsie Schumm and Robert A. Cooke, J. Infect. Dis. **39**:424, 1926.

In a series of forty cases of antral infections from which staphylococci were cultured the presence of bacteriophage was demonstrated in four cases (10 per cent). In eleven cases, the patients were given instillations in the sinuses with a very active lytic agent, but improvement did not result.

Authors' Summary.

Studies on Nutrition in Tuberculosis. II. Experimental Tuberculous Infection in the Albino Rat and the Influence of Vitamin Deficient Diets Thereon. M. I. Smith, E. G. Hendrick, J. Lab. & Clin. Med. **11**:712, 1926.

It is shown that the albino rat experimentally infected with *B. tuberculosis* can be rendered susceptible to tuberculin shock by withholding fat soluble vitamin A from its diet. Experiments are described indicating that the tubercle infected rat deteriorates more rapidly than the noninfected control when maintained on a diet of low biologic value and low in fat soluble A. Liberal allowance of fat soluble A appears to afford protection against the early deterioration. It is not certain whether this indicates a lowered resistance in the albino rat to tubercle infection or an increased demand for vitamin A. The increased susceptibility to tuberculin shock of the infected vitamin A deficient rat appears to offer evidence in favor of the former view.

S. A. Levinson.

The Elective Localization of Bacteria in Heart and Vascular Disease. R. L. Haden, J. Lab. & Clin. Med. **12**:3, 1926.

Forty rabbits were inoculated intravenously with bacteria from the infected teeth of a few patients suffering from heart or vascular disease. Eighty-two per cent of the animals showed some heart lesion; 63 per cent had valvular disease, and 50 per cent showed myocardial involvement. During the same period 1,210 rabbits were injected similarly with cultures from patients not known to have heart or vascular disease. Twenty-two per cent of these had some heart

involvement; 17 per cent had valvular lesions, and 9 per cent had myocardial disease. These results are confirmatory of Rosenow's theory of elective localization. They emphasize, also, the possible relation of the dental infection to the heart disease.

S. A. LEVINSON.

REPORT OF A CASE OF COCCIDIOIDAL GRANULOMA. F. PROESCHER, F. RYAN and A. P. KRUEGER, J. Lab. & Clin. Med. **12**:57, 1926.

A typical case is reported of fatal infection with *Coccidioides imitis* of about six months' duration. Initial symptoms were bronchitis with slight fever, general malaise and debility. Symptoms simulating articular rheumatism followed. Subperiosteal abscesses developed which did not heal or respond to treatment. Blood cultures were positive. Numerous abscesses, particularly over the osseous regions, miliary foci of both lungs, bronchitis, fatty and fibrous myocardial changes and external suppurative pachymeningitis were found post mortem. The various lesions showed typical spore bearing cysts, and inoculation of pus into guinea-pigs produced conditions similar to those seen in the patient.

S. A. LEVINSON.

THE EFFECT OF SANOCRYSIN ON B. TUBERCULOSIS. R. M. FRY, Brit. J. Exper. Path. **7**:174, 1926.

(*a*) In normal human or ox blood or plasma mixed with sodium aurothiosulphate in vitro, concentrations of sodium aurothiosulphate up to 1 in 2,500 did not have any effect on the growth of the tubercle bacillus. Above this concentration the results were rather variable, but in some cases good growth was obtained in concentrations up to 1 in 250, and in one case as high as 1 in 50.

(*b*) The bacillus grows as readily in the plasma of a tuberculous patient taken ten minutes or two days after a dose of 1 Gm. of sodium aurothiosulphate as in the plasma drawn before the dose, or in normal human plasma.

(*c*) The bacillus grows as readily in the plasma of a rabbit after a dose of sodium aurothiosulphate equivalent to 3 Gm. in a human being as in the plasma drawn before the injection.

AUTHOR'S SUMMARY.

EXPERIMENTAL RESEARCH ON ANTHRAX. C. HRUSKA, Ann. de l'Inst. Pasteur **40**:710, 1926.

Attempts at cutivaccination against anthrax with various substances were ineffectual with the exception of a sterilized (formol treated or filtered) edema fluid from a guinea-pig or rabbit dying of anthrax. Protection by the use of this fluid was complete for guinea-pigs. Passing immunity, using defibrinated blood of a cutivaccinated animal, was not realized.

G. B. RHODES.

EXPERIMENTAL RESEARCH ON SCARLET FEVER. CHARLES NICOLLE, E. CONSEIL and P. DURAND, Arch. d. Inst. Pasteur de l'Afrique du Nord **15**:229, 1926.

With a hemolytic streptococcus isolated from the tonsils of a scarlet fever patient, an identical infection was reproduced by tonsillar inoculation in a sensitive normal subject. A reaction was produced in other sensitive persons with the filtered and nonfiltered urine of the same patient, the inoculations being intradermal and subcutaneous.

G. B. RHODES.

RESEARCH ON NATURAL CONJUNCTIVAL GRANULATION IN LABORATORY ANIMALS. CHARLES NICOLLE and UGO LUMBROSO, Arch. d. Inst. Pasteur de l'Afrique du Nord **15**:240, 1926.

All domestic animals are susceptible to granular conjunctivitis, the rabbit and monkey being especially suited to experimental work if they are perfectly free from all natural infections. The authors believe there may be numerous types of human granular conjunctivitis of which trachoma is the most serious and widespread. From its distribution, as well as from the habits of animals found to be most commonly infected, they believe the causative agent may be earth born.

G. B. RHODES.

A NEW CONTRIBUTION TO THE KNOWLEDGE OF EXPERIMENTAL TYPHUS IN RODENTS. CHARLES NICOLLE, Arch. d. Inst. Pasteur de l'Afrique du Nord **15**:267, 1926.

The white rat and mouse, though not manifesting any signs of infection, are suitable animals for the purpose of transportation of the virus of typhus. The guinea-pig, because of its typical temperature curve, is the most reliable indicator of the presence of the virus.

G. B. RHODES.

ANIMALS FOUND TO BE IMMUNE TO TYPHUS IN EXPERIMENTS. CHARLES NICOLLE, Arch. d. Inst. Pasteur de l'Afrique du Nord **15**:276, 1926.

Chickens and toads were found to be immune to typhus.

G. B. RHODES.

PRELIMINARY NOTE ON A NEW INTESTINAL PARASITE INFECTING MAN IN TUNIS. A. ESPIÉ, Arch. d. Inst. Pasteur de l'Afrique du Nord **15**:283, 1926.

The parasite described has been reported before from Egypt, India and Japan. The adult form in this case is unknown, but from the ova and embryos it appears to belong to the suborder of strongylidae, genus *Trichostrongylus*.

G. B. RHODES.

NEW PROCEDURE FOR THE PRODUCTION OF ASPOROGENIC ANTHRAX BACTERIDIA. L. ROSENTHAL, Compt. rend. Soc. de biol. **95**:445, 1926.

The method introduced by Roux to obtain asporogenous strains from the anthrax bacillus by cultivating the bacillus in a medium to which phenol in a certain concentration was added is not always successful. By cultivating sporogenous strains of anthrax in filtrates of bacterial cultures, Rosenthal was able to obtain asporogenous races with all five different strains tried by him.

B. M. FRIED.

IMPENDING ACTION OF ULTRAVIOLET RAYS IN EXPERIMENTAL VACCINATION OF RABBITS. P. CARNOT, L. CAMUS and H. BENARD, Compt. rend. Soc. de biol. **95**:457, 1926.

Rabbits previously irradiated by ultraviolet rays were infected with vaccine. The experiments led to the conclusion that a preliminary irradiation by ultraviolet rays renders the rabbit's skin refractory to the vaccinal eruption. The action is essentially local, since in areas not irradiated cutaneous lesions did appear.

B. M. FRIED.

MALIGNANT ENDOCARDITIS AND ENTEROCOCCUS SEPTICEMIA. ROUSLACROIX, ZUCCOLI and P. MARTIN, Compt. rend. Soc. de biol. **95**:499, 1926.

A case of a malignant endocarditis with repeated positive blood cultures due to the enterococcus is reported in detail.

B. M. FRIED.

THE FREQUENCY OF TUBERCULOSIS. F. HAMBURGER and J. MAYRHOFER-GRÜMBÜHEL, Beitr. z. Klin. d. Tuberk. **63**:778, 1926.

This is a critical survey of the literature on the question. The authors arrive at the following conclusions: 1. A tuberculous infection can be excluded in children if they do not react to 1 mg. of old tuberculin; in adults 100 mg. is necessary. 2. In autopsy work reliable results are obtained only if microscopic studies and animal inoculations complete the macroscopic observations. 3. In order to arrive at a fair representation of the frequency of tuberculosis in the general population, it is necessary to base statistics not on hospital material and to exclude from autopsy records cases of lethal tuberculosis. 4. If such critical methods are used it is found that practically the entire population of civilized countries is infected at the age of from 20 to 25 years. In large cities this complete infection is already accomplished at the age of puberty in the lower social stratum. In smaller towns, in the country and in well-to-do social circles, the infection becomes complete only at a later date. 5. In children the curve of frequency of infection increases evenly with increasing age.

MAX PINNER.

NEWER DISINFECTANTS FOR TUBERCLE BACILLI IN THE SPUTUM. K. W. JÖTTEN and F. SARTORIUS, Beitr. z. klin. d. Tuberk. **63**:831, 1926.

The disinfectant power of a series of newer proprietary products is discussed.

MAX PINNER.

THE FREQUENCY OF HUMAN TUBERCULOSIS. HANS KOOPMANN, Beitr. z. Klin. d. Tuberk. **64**:131, 1926.

On material from 3,041 autopsies the author calculates the frequency of demonstrable tuberculous lesions as not higher than about 40 per cent. The disagreement with the much higher figures of almost any other worker along similar lines is explained by the fact that the Hafenkrankenhaus in Hamburg, where these autopsies were performed, handles almost exclusively emergency cases, mostly of traumatic character, and only a few cases of more or less chronic internal diseases. It is believed, therefore, that a study of this material gives a fairer representation of the average frequency of tuberculosis in the general population than the usual "hospital material."

On the other hand, the author does not mention anything about his autopsy technic. Various studies during the last few years emphasized the fact that only a particularly careful technic will reveal the true number of tuberculous infections. It stands undecided, whether the author's low percentage is due more to the particular nature of his material, or to differences in his technic compared to those of other workers.

MAX PINNER.

STREPTOCOCCIC PANAORTITIS. HANS F. EBERHARD, Centralbl. f. allg. Pathol. u. path. Anat. **38**:261, 1926.

In a man, aged 71, dying of bronchopneumonia there were found at autopsy: an old healed aortic endocarditis with slight fusion of the right and posterior

cusps; an acute inflammatory condition of the aorta close to the aortic cusps characterized by circular circumscribed plaques from 2 to 3 cm. in diameter, composed of gray-red fibrin masses the size of a pinhead, attached to the intima and not associated with thrombi; no noteworthy alteration of the intimal half of the media but in the adventitial half granulation tissue rich in plasma cells, lymphocytes, wide-meshed capillaries and fibroblasts, indicating a hematogeneous origin through the vasa vasorum; and a chronic inflammation in the adventitia and adjacent fat. There was also an embolic nephritis. A nonhemolytic streptococcus was isolated from the kidney and aorta. The Wassermann reaction was slightly positive in the cold with the cholesterin antigen. The second observation was made post mortem on the body of a 65 year old man. There was an old aortic endocarditis with calcification of the wall. All three layers of the aorta were infiltrated with lymphocytes and plasma cells in the affected places, not offering any clue as to the beginning of the process. *Bacillus coli* and a hemolytic streptococcus were cultured from the heart's blood. A Wassermann test was not performed.

GEORGE RUKSTINAT.

THE CULTIVATION OF TUBERCLE BACILLI FROM MICROSCOPICALLY NEGATIVE MATERIAL. F. SCHMIDT and A. SYLLA, Ztschr. f. Tuberk. **45**:370, 1926.

After comparing the results on a number of different mediums it was found that Petroff's egg medium yielded the best results; however, it was not possible to obtain cultures in every case in which guinea-pig infection demonstrated the presence of tubercle bacilli.

MAX PINNER.

FURTHER INVESTIGATIONS ON BACILLUS PROTEUS. SHIGERU MATSUI, Tohoku J. Exper. Med. **7**:544, 1926.

Of 172 strains of proteus bacilli from man, rats, mice, guinea-pigs and other animals, forty-four were found inagglutinable by nine standard serums and several Proteus X serums. Among the remaining thirty-five strains three cultural types were distinguished, and after cross agglutination tests with antiserums for certain of these strains, in which only a few cultures reacted up to the full titer of the serum, the conclusion was made that there were many varieties of *Bacillus proteus,* and that atypical cultures with coli-like colonies and without proteolytic ferments could hardly be differentiated from atypical *Bacilli coli.*

E. B. PERRY.

Immunology

THE NATURE OF THE TOXIN-ANTITOXIN FLOCCULATION PHENOMENON. J. J. BRONFENBRENNER and PHILIP REICHERT, J. Exper. Med. **44**:553, 1926.

Animals immunized with the formalinized filtrates of young toxic cultures of *Bacillus botulinus* produce an antitoxic serum poor in precipitins.

Animals immunized with the formalinized filtrates of old and partly autolyzed toxic cultures produce an antitoxic serum containing precipitins.

Animals immunized with toxin-free autolyzed bacteria produce a serum free from antitoxin but rich in specific precipitins.

Animals immunized with the filtrates of an atoxic variant produce a serum free from antitoxin but rich in precipitins for the homologous toxin.

Animals immunized with the washed bacteria of the atoxic variant produce a serum that does not contain any antitoxin, but is rich in precipitins for the homologous toxin.

Removal of the precipitins by flocculation with a nontoxic antigen does not materially reduce the antitoxic value of a serum.

Removal of the proteins of the antigen by acid coagulation removes the specific precipitable substance.

All the serums that contain precipitins produce the specific flocculus when combined with homologous toxins, anatoxins or the filtrates of the atoxic variant. The flocculation is restricted within the type. The amount of the precipitate and the width of the zone vary approximately with the estimated amount of bacterial protein in the antigen that is used for the immunization of animals.

It is concluded, therefore, that the toxin-antitoxin flocculation is a specific bacterial precipitation phenomenon.

AUTHOR'S SUMMARY.

A CONTRIBUTION TO THE THEORY OF PHAGOCYTOSIS. ERIC PONDER, J. General Physiol. **9**:827, 1926.

In a discussion, almost entirely mathematical, of the influence of surface forces on phagocytosis, Ponder shows that Tait's discussion of surface contact angles deals with two only of five possible cases. The greater part of the article is concerned with the possible influence of electrical charge, and the writer demonstrates how this may be an agency in phagocytosis, even where cell and particle are of like charge, as is usually the case.

H. E. EGGERS.

ON THE SEROLOGICAL RELATIONSHIP OF ACID-FAST BACTERIA. J. FURTH, J. Immunol. **12**:273, 1926.

There are qualitative differences in the antigenic structure of various acid-fast bacilli. These differences cannot be demonstrated clearly by the direct agglutination tests because of the complete or partial inagglutinability of most of the acid-fast bacilli. Complement fixation and absorption experiments can be successfully applied to the antigenic analysis of this group of organisms. Inagglutinability of acid-fast bacilli is doubtless due in part to a physicochemical interference with flocculation, but it is probable that all receptors detectable by complement fixation are not involved in the formation of flocculi. Mammalian tubercle bacilli have an antigenic structure different from all other acid-fast bacilli. Differentiation within the mammalian group has not been found possible thus far. One atypical bovine strain is an exception to this statement. Avian tubercle bacilli likewise differ qualitatively from all other microorganisms but they do not form a homogeneous group, for there are at least three avian subtypes. The nonchromogenic strains isolated from patients with leprosy by Kedrowsky and by Duval, and the agglutinable culture of Arloing, belong in this group. A serologically distinguishable group of acid-fast bacilli from coldblooded animals does not exist. In antigenic structure these micro-organisms show little similarity to each other and to other acid-fast bacilli. Acid-fast saprophytes differ qualitatively from all other acid-fast bacteria. Within the saprophytic acid-fast group there is at least one fixed subtype, for strains from various sources such as those designated "Smegma," "Mist," "Milk," "Pseudotuberculosis" and "Butter R" have been found to be closely related if not identical. These observations disprove the hypothesis that acid-fast bacilli possess a common antigen present in varying proportions in various strains, but they show that qualitative differences occur and suggest the possibility that serologic methods may be used to identify acid-fast micro-organisms.

AUTHOR'S SUMMARY (S. A. LEVINSON).

HETEROLOGOUS CORPUSCLAR ANAPHYLAXIS. R. R. HYDE, J. Immunol. **12**:309, 1926.

The author attempts to demonstrate corpuscular anaphylaxis and disposes of the claim that the phenomenon is due to the introduction of small amounts of serum with the corpuscles. Sheep corpuscles sensitize guinea-pigs to chicken corpuscles, and since sheep serum does not sensitize guinea-pigs to chicken serum the conditions for serum anaphylaxis are excluded; chicken cells sensitize rabbits to sheep and goat cells, but sheep cells do not sensitize rabbits to chicken cells. Sheep and goat cells sensitize guinea-pigs to chicken cells but chicken cells do not sensitize to sheep and goat cells. Anaphylaxis in the rabbit follows the behavior of the hemolytic antibody in its action toward chicken, sheep and goat cells. The phenomenon does not follow the behavior of the agglutinin toward these cells. In the guinea-pig anaphylaxis does not follow the behavior of either the agglutinins or the hemolysins toward the red cells of the chicken, sheep and goat. The death obtained in the guinea-pigs with the red cells was typical of anaphylactic shock, as evidenced by the onset of symptoms, the violent death and autopsy observations.

S. A. LEVINSON.

A STUDY OF TETANUS AGGLUTININS AND ANTITOXIN IN HUMAN SERUMS. GEORGE E. COLEMAN and K. F. MEYER, J. Infect. Dis. **39**:332, 1926.

Of 104 human serums studied, twenty-one did not show agglutinins in dilutions of 1:10 or higher; fifty-three (50.9 per cent) contained this antibody in dilutions of 1:20 or higher, and seventeen (16.3 per cent) at 1:40 to 1:60.

Agglutinins occurring in serum diluted 1:40 are assumed to be diagnostic for *Clostridium tetani*. In this dilution or higher type 5 was found eleven times (55 per cent); type, 2, five times (25 per cent), and type 1, four times (20 per cent).

The serum of a single person may agglutinate as many a five types of *Clostridium tetani*.

Antitoxin was not found in serums irrespective of the presence or absence of agglutinins.

AUTHOR'S SUMMARY.

THE PRECIPITIN REACTIONS OF EXTRACTS OF VARIOUS ANIMAL PARASITES. LUDVIG HEKTOEN, J. Infect. Dis. **39**:342, 1926.

The results of these experiments indicate, as expected, that the precipitin reactions of materials derived from animal parasites follow the general law of species-specificness. The only exception to this rule seems to be the reaction of extract of *Setaria equina*, which in its classification is far removed from the ascarids, with precipitin serum against ascaris albumin. To establish definitely the interrelations of the precipitin reaction in this case requires, however, additional observations. It is of particular interest to note that all the extracts giving precipitin reactions with the serum against ascaris albumin were found by Ransom, Harrison and Couch to cause skin reactions in a person sensitive to ascaris. Extension of the study of animal parasites by immunologic methods is indicated. Pathogenic forms, for example *Dibothriocephalus latus* in particular, should be given attention.

AUTHOR'S SUMMARY.

SOME INFLUENCES OF ANTITOXIN AND OTHER SERUMS ON BOTULINUM INTOXCATION. L. B. JENSEN, J. Infect. Dis. **39**:413, 1926.

The toxicity of one minimum lethal dose of type B botulinum toxin is commonly nullified when mixed and incubated at 20 C. for one hour with large

amounts of type A antitoxin before introduction into test animals or when the toxin and serum are given separately within an interval of sixty minutes.

Large quantities of type C antitoxin lessen the potency of one minimum lethal dose of type B toxin.

Type A toxin seems to be neutralized only by its homologous antitoxin.

An adjuvant action is elicited in white mice by the following mixtures: type A toxin + B antitoxin, type A toxin + C antitoxin, and type A and B toxins with diphtheria or tetanus whole antitoxins, sporogenes filtrate antiserum and normal rabbit or sheep serums.

AUTHOR'S SUMMARY.

UNION BETWEEN ANTIGEN AND ANTIBODY IN THE WASSERMANN TEST. S. L. LEIBOFF, J. Lab. & Clin. Med. **11**:1164, 1926.

Saturation of the double bonds in the fatty acids of the lipoidal antigen used for the complement-fixation test in the diagnosis of syphilis does not materially interfere with its antigenic properties; hence, the unsaturated fatty acids in the lipoid molecule are not responsible for the specificity of the Wassermann reaction. Blocking off the hydroxyl groups in the lipoid molecule by substituting acetyl groups does not materially impair the antigenic value of the lipoid. Since chemical union would most likely take place either at the double bonds of the unsaturated fatty acids or at the hydroxyl groups, and the blocking of both of these possibilities does not materially diminish the specific value of the antigen, it follows that the Wassermann reaction is probably not based on a chemical reaction, but rather that physical phenomena are involved in it.

S. A. LEVINSON.

THE INFLUENCE OF OPTIMAL PROPORTIONS OF ANTIGEN AND ANTIBODY IN THE SERUM PRECIPITATION REACTION. H. R. DEAN and R. A. WEBB, J. Path. & Bact. **29**:473, 1926.

The speed of particulation in a mixture of horse serum and homologous antiserum is dependent on the relative proportions of the two ingredients.

In a series of tubes containing a constant volume of antiserum and various volumes of horse serum the volume of horse serum most favorable to rapid particulation has been determined, and differences as small as 0.0001 cc. of horse serum have been detected.

By the method of titration which has been described, the antibody ratio of any particular antiserum can be expressed as a figure.

Thirty specimens of antiserum have been examined. The highest antigen-antibody ratio was 1 to 177, the lowest 1 to 14.

The ratio determined with an antiserum and a specimen of normal horse serum has been found to hold good for specimens of horse serum from other normal horses.

The method can be employed for the quantitative estimation of either antigen or antibody.

The greatest weight of precipitate which can be obtained from any volume of an antiserum is obtained by adding a volume of horse serum greater than that which is found to produce the most rapid formation of particles.

AUTHORS' SUMMARY.

ZONE PHENOMENA IN VIVO TRYPANOLYSIS. WILLIAM H. TALIAFERRO and THURSTON L. JOHNSON, J. Prevent. Med. **1**:122, 1926.

Serum taken from guinea-pigs or rabbits after infection with *Trypanosoma equinum* and after the first trypanolytic crisis, or from infected sheep during

the chronic infection, will often produce a trypanolytic crisis in mice previously infected with the passage strain. The length of life of mice treated in this manner is prolonged over that of untreated mice approximately the same number of days that the artificial crisis lasts.

In mice infected with the passage strain and given a series of increasing doses of immune serum, some doses will often produce a crisis while larger doses are not effective. There may be several recurring "zones of inhibition" of lytic function within a single series.

Zonal phenomena are not dependent on inactivation. They occur with trypanolytic serums arising during the uninfluenced course of infections in guinea-pigs, rabbits and sheep, and in infected mice after treatment.

Zonal phenomena were not observed in either fresh or inactivated normal human serum, which is markedly trypanocidal in vivo.

The therapeutic value of immune trypanolytic serum, as measured by the length of life of the mice, is dependent on the occurrence of trypanolysis and not on the size of the dose. Thus, when trypanolysis is inhibited in a larger dose, length of life is not increased over the control, whereas in smaller doses with trypanolysis, it is increased. Furthermore, the increase in length of life is approximately the same whether the crisis was brought about by a small or a large dose of immune serum.

AUTHORS' SUMMARY.

THE TITRATION OF TETANUS TOXIN AND ANTITOXIN BY THE FLOCCULATION METHOD. G. ABT and B. ERBER, Ann. de l'Inst. Pasteur **40**:659, 1926.

Antitetanus serums, if they flocculate at all, can be titrated by this method with a saving of time and animals. Those weaker serums which seem to have an element inhibitive to flocculation, possibly a "colloid protector," can be titrated by the usual animal method.

G. B. RHODES.

ATTENUATION AND ANTIGENIC POWER OF DIPHTHERIA ANTITOXIN TREATED BY VARIOUS SUBSTANCES. DR. PAUL NÉLIS, Ann. de l'Inst. Pasteur **40**:666, 1926.

Diphtheria toxin dialyzes very little through a collodion membrane, but the toxin which has been dialyzed loses its toxic power rapidly and completely if left in the incubator for an extended period. Ozone destroys the toxin partially. More rapid destruction is brought about by small quantities of sodium oleate at incubator temperature, and by quinine dihydrochloride or quinine bisulphate, the toxin being permanently destroyed by these chemical agents. In all of these cases the toxin which has been modified retains, in varying degrees, its antigenic property, anatoxin being the most active as an immunizing agent. In the preparation of anatoxin it was found that the formol fixes in large part on the dialyzable substances foreign to the toxin.

G. B. RHODES.

IMMUNIZATION WITH THE HEATED SERUM OF THE EEL. L. CAMUS and E. GLEY, Compt. rend. de la Soc. de biol. **95**:535, 1926.

In 1898 Phisalix noted that heated serum of the eel immunizes the guinea-pig against the venin of the viper. Camus and Gley were also able in 1898 to immunize rabbits against a toxic serum by preparing these animals with a homologous serum heated at from 55 to 58 C. for fifteen minutes. They then concluded that a toxic serum (it concerned in these experiments the serum of the eel—one of the most toxic known) rendered atoxic by heat preserves its immunizing properties.

The injection of this serum leads to the formation of an antitoxin just as if the animal were immunized repeatedly with small doses of the toxin itself.

This report concerns itself with analogous experiments with a toxic serum of the muraena *(Muraena helena)*. Careful experiments with this toxin have confirmed those reported previously by Phisalix, and by Camus and Gley.

B. M. Fried.

Localization in Scalp of Metastases of Mammary Carcinoma. G. Riehl, Jr., Arch. f. klin. Chir. **140**:320, 1926.

A woman who had undergone operation for scirrhus carcinoma of the breast six years previously, had falling of the hair over a number of small circular areas on the scalp. The skin was not discolored but, on palpation, flat, hard lumps were found in it which proved to be carcinomatous and of the same structure as that of lenticular metastases in the vicinity of a breast carcinoma. Riehl found but one similar case — that of Arndt — in the literature.

The Significance of the Heterogenetic Tuberculin Allergy for the Development of Tuberculin Sensitiveness. A. Adam, Beitr. z. Klin. d. Tuberk. **63**:635, 1926.

Tuberculin sensitiveness can be produced in guinea-pigs with killed tubercle bacilli: it can be transmitted by the injection of organ-suspensions of such artificially sensitized animals. The injection of organ-suspensions from normal animals produces tuberculin sensitiveness in some instances. Infants could be made tuberculin sensitive by means of treatment with a coli vaccine. On the basis of these experiments the nonspecificity of tuberculin allergy is emphasized.

Max Pinner.

The Production of Local Tuberculin Sensitiveness in Guinea-Pigs and in Man. H. Fernbach, Beitr. z. Klin. d. Tuberk. **63**:730, 1926.

Guinea-pigs which received from 1 to 3 mg. of killed bacilli intraperitoneally developed, in about 50 per cent of the cases, a definite skin hypersensitiveness against tuberculin, which lasted in some cases almost two years. Children not infected with tuberculosis received 1 mg. of killed human tubercle bacilli into lymph glands during the inflammatory reaction following smallpox vaccination. A certain percentage of the children developed a typical skin sensitiveness to tuberculin. The experiments were performed on idiotic children. The intramuscular injection of the same amount of killed tubercle bacilli did not produce a skin hypersensitiveness.

Max Pinner.

The Specificity of the Tuberculin Reaction. K. Zieler and J. Hämel, Beitr. z. Klin. d. Tuberk. **63**:991, 1926.

Minimal doses of tubercle bacillus derivatives produce positive skin reactions only in human beings infected with tuberculosis. Other bacterial products (from coli or dysentery bacilli) make positive reaction both in tuberculous infected and noninfected human beings. Coli toxin is apparently a vascular poison and produces a paralysis of the capillaries at the site of infection for a long period. This explains the fact that one may observe exacerbations of coli skin reactions after the injection of tuberculin; likewise, many nonspecific stimuli will produce an acute inflammatory reaction on tuberculous foci.

Max Pinner.

THE SPECIFICITY OF THE TUBERCULIN REACTION AND ITS HISTOLOGIC CHARACTER. K. ZIELER, Beitr. z. Klin. d. Tuberk. **64**:94, 1926.

The local response to the subcutaneous or intradermal introduction of substances which are not easily resorbed or digested is the formation of tuberculoid tissue. It is, therefore, not justifiable to compare reactions produced by nonspecific bacterial bodies with those produced by old tuberculin. The injection of nonspecific bacterial culture filtrates produces only a nonspecific granulation tissue. Although a variety of substances may produce tuberculoid tissue, the tuberculin reaction is strictly specific, since tuberculin produces true tuberculoid tissue only in the tuberculous infected organism.

MAX PINNER.

CONCERNING THE DIFFERENTIATION OF ALBUMINOUS SUBSTANCES IN THE SPINAL FLUID BY MEANS OF PRECIPITATION. V. KAFKA, Ztschr. f. d. ges. Neurol. u. Psychiat. **101**:245, 1926.

Cats were treated with various globulin fractions of Wassermann positive and negative serums. The serum of each cat was then used in precipitin reactions with the spinal fluids of patients with general paralysis, of normal patients and of those with tuberculous meningitis, and various curves were obtained.

ROY GRINKER.

BLOOD GROUPING OF LAPLANDERS IN SWEDEN WITH DESCRIPTION OF TECHNIC. E. D. SCHÖTT, Hygiea **88**:480, 1926.

The number of persons examined was 183, of which 35.5 per cent belonged to group 1 (Jansky), 52.5 per cent to group 2, 7.7 per cent to group 3 and 4.4 per cent to group 4.

AUTHORS' SUMMARY.

Tumors

REPORT OF A CASE OF CHORIOCARCINOMA OF THE UTERUS COMPLICATING PREGNANCY. J. J. GILL, Am. J. Obst. & Gynec. **12**:203, 1926.

Gill describes a case of choriocarcinoma occurring in a secundipara, aged 18, whose chief symptom was profuse vaginal bleeding. The surface of the specimen was studded with masses the size of a pinhead, and the wall was infiltrated with soft nodules. The cavity of the uterus contained a 5-month old fetus. Microscopically, the chorionic villi did not show any evidence of cystic degeneration, and nests and cords of Langhans cells without syncytial covering could be seen infiltrating the myometrium, destroying the muscle fibers.

A. J. KOBAK.

CARCINOMA OF CORTEX OF SUPRARENAL GLAND WITH VIRILISM. H. M. FEINBLATT, Arch. Int. Med. **38**:469, 1926.

A young woman progressively developed virile characteristics, including facial hypertrichosis, the masculine type of abdominal and axillary hair, a low pitched voice and a masculinoid facies. Later, a tumor was palpated in the region of the right kidney. Necropsy revealed a large carcinoma of the cortex of the right suprarenal gland, with extension by way of the vena cava but without distant metastasis.

S. A. LEVINSON.

GIANT CELL TUMORS NOT CONNECTED WITH BONES. L. D. CAMPBELL, California and West. Med. **25**:212, 1926.

The tumors are benign, affect both sexes equally, occur most often between the ages of 10 and 20 years, are preceded by trauma or inflammation about one third of the time and are treated successfully by excision. Macroscopically they are encapsulated, lobulated, gray to yellow-pink nodules, at times mottled with brown, hemispherical and rarely as large as an egg. Microscopically the dense fibrous capsule and trabeculae are infiltrated with tumor cells, contain pigment deposits and in places are hyalinized. The giant cells are from 9 to 100 microns in diameter and contain from two to one hundred nuclei placed centrally. About one half of the tumors contain xanthoma cells with distinct cell membranes, small dark nuclei and a pale cholesterin containing cytoplasm. Blood vessels are abundant and often show signs of endothelial proliferation. Degenerative changes are constant and usually consist of cholesterin and hemosiderin deposits.

Campbell cites three new cases. The first two occurred on the tendons of the ring and index fingers of two women, aged 60. The third occurred in a man, aged 40, and apparently had its origin in the laryngeal cartilages.

GEORGE RUKSTINAT.

THE NATURE OF THE "OAT-CELLED SARCOMA" OF THE MEDIASTINUM. W. G. BARNARD, J. Path. & Bact. **29**:241, 1926.

The author examined nineteen cases of malignant tumor of the lung and mediastinum. Of this number seven were obviously carcinomas; the others were of the type usually classified as "oat-celled sarcoma." In the obvious carcinoma "oat cells" were found as well as the usual carcinoma cells, while in the twelve cases consisting largely of "oat-cells," large polygonal cells and tubules lined by cuboidal or columnar cells were seen. Aside from the squamous-celled carcinoma there is not any essential difference in macroscopic appearance or distribution between obvious carcinoma and "oat-celled tumors." The author therefore considers the so-called "oat-celled sarcomata" of the posterior mediastinum as medullary carcinoma of the bronchi.

E. M. HALL.

FURTHER OBSERVATIONS ON A FLOCCULATION REACTION FOR THE SERUM DIAGNOSIS OF MALIGNANT DISEASE. H. J. B. FRY, J. Path. & Bact. **29**:353, 1926.

A saline emulsion of the saline-insoluble, acetone-insoluble, alcohol-soluble substances of tumor tissue gives a flocculation reaction with the serums of cases of malignant disease.

In 1,000 malignant and control cases 748 correct results were obtained (74.8 per cent). In the 494 cases of malignant disease there were 357 correct results (72.3 per cent) and the 506 controls gave 391 correct results (77.3 per cent).

Healthy persons and pregnant patients gave negative reactions except in two cases each. Nonmalignant tumors gave a negative reaction in 72 per cent. Syphilis, tuberculosis and certain conditions of cellular disintegration cause flocculation in a percentage of cases.

If tuberculosis, syphilis and suppurative conditions are excluded, a positive reaction has considerable weight in the diagnosis of malignant disease.

A negative reaction is of less value, but generally indicates that malignant disease, if present, is neither advanced nor widespread.

A strongly positive reaction seems to indicate advanced malignancy or widespread metastases.

The reaction is not completely specific for malignant disease, but is an indication of tissue or cellular disintegration.

AUTHOR'S SUMMARY.

A CASE OF OSTEOCLASTOMA (MYELOID SARCOMA, BENIGN GIANT CELL TUMOR) WITH PULMONARY METASTASIS. E. F. FINCH and H. H. GLEAVE, J. Path. & Bact. **29**:399, 1926.

A case of osteoclastoma (myeloid sarcoma) of the lower end of the femur is reported, of at least nine years' duration, in which metastasis to the lungs has taken place.

The metastases have the histologic characters of the primary tumor, with numerous typical giant cells and in addition an admixture of fibrosarcomatous tissue.

This case, and other cases from the literature to which reference is made, confirm the neoplastic character of these tumors, and do not leave any doubt that, though usually slow-growing and only of local malignancy, they are essentially sarcomatous.

AUTHORS' SUMMARY.

CANCER OF THE STOMACH AND WILD RAT INFECTION WITH NEMATODE WORM, HEPATICOLA GASTRICA BAYLIS, 1925. C. BONNE, J. Trop. Med. **29**:288, 1926.

This is the fourth case of cancer in the cardiac portion of the stomach in rats associated with hepaticola gastrica.

PIGMENTED NEVI ARE NERVE TUMORS. P. MASSON, Ann. d'anat. path. **3**:417, 1926.

The histogenesis of these tumors has been the object of numerous investigations. Von Recklinghausen traced the origin of the nevus cells to the endothelium of the lymphatics and designated the tumors as lymphangiofibromas. Ribbert considered the nevus cell as mesodermal in origin, but "specialized" to produce pigment. The connective tissue origin of the nevus cell is supported by Israel, Lubarsch and Jadasson. Finally, Unna claims that the nevus cell is epidermal in origin. The latter theory has been supported by Bloch, Darier and others.

Masson attempts to show that nevus is of nervous origin. The "neuronevus" of the scalp, according to Masson, arises from a localized proliferation of a group of elements of neurogenous origin, connected with the myelinic nerves of the derma. These elements are capable of differentiating in satellite elements typical of certain tactile terminations, particularly under the form of the corpuscles of Wagner-Meissner and the cells of Merkel-Ranvier.

A comparative study of the cells of Merkel-Ranvier and the epithelioid nevus cells on one hand, and the cells of Langerhans on the other, has impressed Masson with the idea that these elements, united by intermediary forms, are all functional adaptations of the same strain of cells. The cells of Langerhans or the epidermic melanoblasts in man are related to the tactile cells and the neuroglia of the tactile nerves.

In the second article Masson develops in detail his ideas concerning the relation of pigmented nevus of the scalp to nevus elsewhere. He affirms that there is not any distinction whatever between different forms of pigmented nevus. They all are terminal neuromas of the tactile nerves.

B. M. FRIED.

THE INCREASE IN FREQUENCY OF CANCER, IS IT REAL OR APPARENT? LÉON IMBERT, Bull. et de l'Ass. franç. p. l'etude du cancer **15**:141, 1926.

Imbert has investigated the incidence of cancer in the Municipal Hospital (Hôtel-Dieu) of Marseille (France) from 1870 to 1925. As elsewhere the first examination of figures showed an obvious increase in the incidence of cancer. Thus there were only eleven cancers in 1,000 patients admitted in the years from 1871 to 1925 and forty for every 1,000 in the years from 1920 to 1924.

Imbert then went into the following details: He has classified the cancer material of the Hôtel-Dieu into two groups:

1. This group included cancers known to physicians "from time immemorial" (the "old cancers"), i. e., carcinoma of the uterus, vagina, breast, tongue and face.

2. These cancers were those, the diagnosis of which has made immense progress in recent years (the new cancers). His results are to the effect that the incidence of the "vieux cancers" has remained stationary or even decreased, while that of the "new cancers" has considerably increased. His figures are as follows:

THE "OLD CANCERS"

Incidence in cancer of the uterus and vagina has decreased from 30 to 18 per cent.

Incidence in cancer of the face has decreased from 16 to 8 per cent.

Incidence in cancer of the tongue has decreased from 6.8 to 6 per cent.

Incidence in cancer of the breast has remained stationary—7 per cent.

THE "NEW CANCER"

Incidence in cancer of the stomach has increased from 8 to 15 per cent.

Incidence in cancer of the rectum has increased from 3 to 5 per cent.

Incidence in cancer of the vaso-urinary has increased from 3.6 to 6.5 per cent.

Incidence in cancer of the larynx has increased from 2.2 to 7.8 per cent.

The following point in Imbert's investigation is of interest: "If we are to consider," says the author, "that cancer is really increasing, this should be noted in *old* as well as in *young* age." Hence, he has divided his material in decades, investigating the occurrence of cancer between the ages of 20 and 30, 30 and 40, 40 and 50, 50 and 60, etc., respectively. His figures show clearly that the occurrence of cancer between the ages of 20 and 30 remained stationary (4.6 per cent), between the ages of 30 and 40 it has even decreased (from 17.7 to 12.6 per cent). Between 40 and 50 it occurred in 28.7 per cent in the first 25 years and 26.3 per cent in the second, respectively; between 50 and 60 it occurred in 28.3 and 28.7 per cent; between 60 and 70 in 17.8 and 19.2 per cent; between 70 and 80 in 5.8 and 8.5 per cent. His observations are to the effect that in the age below 50 cancer has decreased, while above that age it has increased, apparently because of the fact that human life has considerably increased.

"A certain number," he says, "of cancer candidates have succumbed to some other disease which has attacked them at an earlier age."

B. M. FRIED.

TUBERCULOSIS OF THE AXILLARY LYMPH NODES IN TUMORS OF THE MAMMARY GLAND. P. PYRM, Beitr. z. Klin. d. Tuberk. **63**:900, 1926.

In seven cases of carcinoma and in one case of myxosarcoma of the mammary gland, tuberculosis of the axillary lymph nodes was observed without any demonstrable tuberculous lesion along the upper extremity or in the mamma. Four of these cases showed at the same time tumor metastases in the tuberculous lymph

nodes. The tuberculous disease of the axillary lymph nodes does not have any casual connection with the mammary tumor; but indicates a pulmonary lesion. The lymph nodes become infected by direct lymphogenous propagation through the pleura. In cases of metastasis and tuberculoid nodules in the lymph nodes Herxheimer's "pseudo-tubercules" must be considered.

MAX PINNER.

CHLOROMA OF THE DURA MATER WITH ATYPICAL SYMPTOMS. H. ROTHSCHILD, Deutsche Ztschr. f. Nervenh. **91**:57, 1926.

A case was studied which revealed two chloromas; one pressing deeply on the right frontal lobe, the other over the left parietal lobe.

ROY GRINKER.

CONCERNING DIFFUSE SARCOMATOSIS AND GLIOMATOSIS IN THE MENINGES OF THE CENTRAL NERVOUS SYSTEM. O. SCHUBERTH, Deutsche Ztschr. f. Nervenh. **93**:34, 1926.

Fifty-six cases of diffuse sarcomatosis and twenty of diffuse gliomatosis of the meninges are gleaned from the literature. The author reports three of his own cases. He considers the sarcomas primary in the meninges with invasion into the nervous tissue, with the result that the small round cell sarcoma often resembles encephalitis.

ROY GRINKER.

A CONTRIBUTION TO THE LIPOMAS OF THE UTERUS. HANS DWORZAK, Frankfurt. Ztschr. f. Path. **34**:20, 1926.

Twenty-one cases of lipoma of the uterus have been reported in the literature. Of this number only a few were true lipomas, since most of them contained in their stromas admixtures of muscle and connective tissue. Four of the twenty-one cases reported were sarcomas.

The author reports two cases, one in a woman, aged 75. A well encapsulated, fatty tumor 4 cm. in diameter was found near the left tubal cornu in the submucous tissue. Histologically it proved to be a true lipoma. The second patient was a woman, aged 69, who had a tumor 3 cm. in diameter also located near the left tubal cornu. Histologically this tumor was composed of fat cells, with strands of smooth muscle and connective tissue scattered through the fat, therefore a lipofibromyoma.

E. M. HALL.

EXPLANTS OF ROUS SARCOMA. F. WIND, Klin. Wchnschr. **5**:1355, 1926.

The lactic acid production of Rous sarcoma cultures is lower (3 per cent of the dry weight per hour) in the clotted plasma than in serum, because the slower diffusion of the acid inhibits the reaction. The sarcoma grew for forty-eight hours even in complete absence of oxygen and could be transplanted under such conditions twice more before it died. The presence of dextrose is one of the important factors. The culture grew somewhat more slowly with a concentration of 0.007 per cent dextrose in an atmosphere of 95 per cent oxygen and 5 per cent carbon dioxide. With 0.2 per cent dextrose added to a dialyzed medium the growth was normal down to 0.4 per cent oxygen. In the absence of oxygen, addition of dextrose did not restore the quality of a dialyzed medium. This shows that some other dialyzing substance is necessary for strictly anaerobic growth.

THE RESISTANCE OF THE ERYTHROCYTES AND DIAGNOSIS OF CANCER. E. COHNREICH, Klin. Wchnschr. **5**:1650, 1926.

A markedly increased osmotic resistance of the erythrocytes is demonstrated in eighty-three of ninety-three patients with intestinal carcinoma. Obstructive icterus is the only other disease that produces this; even extra-alimentary carcinoma does not. The theory is developed that there is a fundamental difference between the carcinomas of the organs derived from the embryonic endoderm and those of the organs from the mesoderm and ectoderm. ROY GRINKER.

ADVANCES IN THE TREATMENT OF CANCER: I. CLINICAL PART. E. OPITZ, K. VORLÄNDER and H. JUNG, München. med. Wchnschr. **73**:1567, 1926. II. EXPERIMENTAL PART, ibid. **73**:1624, 1926.

Striking results are obtained with calcium, silicon, phosphoric acid, hypophosphorus acid, epinephrine hydrochloride, choline, cerium and trypan blue in cancerous rats and patients. There is necrosis of the tumor cells, slow disappearance of lactic acid, and relief of acidosis. Normal metabolic processes are reestablished and the loss of glucose is limited, thus relieving the cachexia.

J. D. WILLEMS.

ENDOTHELIOMATOUS INFILTRATION OF THE ENTIRE SPINAL PIA AND OF THE PIA OF THE BASE OF THE BRAIN. Neurol. Festschr. f. Prof. G. Rossolimo, 1925, p. 544.

A case of this description is reported. J. D. WILLEMS.

Medicolegal Pathology

THE PSYCHIATRIC EXAMINATION OF PRISONERS IN MASSACHUSETTS. W. OVERHOLSER, Boston M. & S. J. **195**:1065, 1926.

Overholser describes the advanced position taken by Massachusetts in the psychiatric examination of prisoners, the latter term referring to persons legally detained, whether awaiting trial or serving sentence. Under a law dating back in its original form to 1849, any person under complaint or indictment may, at the time set for sentence or any time prior thereto, be committed to a state hospital as insane or for observation as to his mental condition. The experts who make the recommendation of commitment are employed by the court and act as advisors of the court. The courts also accept recommendations from the state hospitals as to release, after recovery, of persons committed for observation, or as to their further detention. A law passed in 1918 obviates the necessity of observation commitment in all doubtful cases by authorizing any court to request the department of mental diseases to assign a member of the staff of a state hospital to make an examination of any person coming before the court, a provision applicable even to the plaintiff. Fees are not paid for such examinations, and the courts are not hampered by the fear of expense in making their requests for mental examination. Examination under the provisions of the foregoing laws rests with the discretion of the court. A law passed in 1921 and amended in 1925 makes it mandatory on clerks of court to report to the department of mental diseases all persons (1) accused of a capital crime (murder in the first degree); (2) indicted or bound over for a felony who (*a*) have been previously convicted of a felony, or (*b*) have been previously indicted for any other offense more than once. On the receipt of the report the depart-

ment assigns two psychiatrists who examine the prisoner and for a legal fee of $4 report regarding his mental condition and the "existence of any mental disease or defect which would affect his criminal responsibility." This psychiatric report is forwarded to the court and is available not only to the latter but also to the district attorney and the council for the defense. The report is not admissible as evidence, but the examining psychiatrists may testify as to their observations, and either side may present additional expert testimony. The foregoing laws do not make any provision for the examination of prisoners who may receive local jail, rather than state prison, sentences for minor offenses, a group of offenders who are often repeaters and recruit the ranks of more serious offenders. In 1924 there was passed by the general court an act calling for psychiatric examination, by the department of mental diseases, of convicted persons serving, in a house of correction or jail, sentences of more than thirty days (except for nonpayment of fine) and of all persons in such institutions known to have served a previous sentence. It is hoped that publication of the valuable data which will undoubtedly result from the mental examination of prisoners under the laws of Masachusetts will lead to the adoption of similar intelligent and humanistic laws in other states.

O. T. Schultz.

Observations on Six Anomalous Bloods, with Reference to the Theory of Iso-Agglutination. S. C. Dyke, Brit. J. Exper. Path. **7**:294, 1926.

For the purpose of detecting anomalous iso-agglutination reactions, a series of 120 successive bloods was examined by testing all available serums against all available corpuscles, by cross agglutination in groups of twelve bloods, and by agglutinin absorption experiments. Six anomalous bloods were encountered; on first examination four of these appeared to belong to group II, the remaining two to group III. The view being accepted that the presence of the agglutinable factors A and B in the cells is the criterion of group I blood, further examination proved the six anomalous bloods to belong to group I. The anomalous reactions were due apparently to the low titer in agglutinins *a* and *b* of the serums used for the first typing. The author accepts the older view of the dependence of iso-agglutination on two allelomorphic characters which are transmitted as mendelian dominants, and does not consider it necessary to adopt the more recent view of multiple allelomorphs to explain anomalous iso-agglutination reactions The author concludes that in the absence of absorption tests many group I bloods will escape detection, a fact which accounts for the apparent rarity of bloods of group I, and one which is important in the medicolegal application of iso-agglutination and in the matching of bloods for transfusion.

O. T. Schultz.

Technical

Quantitative Estimation of the Total Protein Content in Cerebrospinal Fluid. G. A. Young and A. E. Bennett, Am. J. M. Sc. **172**:249, 1926.

In making 600 quantitative estimations of protein in cerebrospinal fluid by precipitating by alcohol, acidifying with acetic acid, heating and measuring resultant precipitate volumetrically in capillary tipped vaccine tubes and reading in milligrams per hundred cubic centimeters, it was found that normal spinal fluid varies from 25 to 75 mg. of protein per hundred cubic centimeters, borderline cases from 75 to 100 mg. per hundred cubic centimeters, and definite increase

occurred in pathologic conditions in which the qualitative globulin test was negative or doubtfully positive. In neurosyphilis the determination was of value in estimating serologic improvement under treatment. The method used was found to be subject to slightly greater error than the Denis Ayer method but sufficiently accurate for clinical purposes.

RUTH TAYLOR.

TABLE FOR LACTOSE (MILK OR URINE) AND GLUCOSE (BLOOD OR URINE) CALCULATION. H. D. HASKINS, Am. J. M. Sc. **172**:256, 1926.

A table is given in which readings of the sugar content of such fluids as blood, urine or milk, as determined by titrations with a special thiosulphate solution, are converted directly into percentages. The table can be used only with the author's modification of the Schaffer Hartman method. The lactose of milk or urine can be estimated easily and accurately with the same reagents and technic as are used for the estimation of glucose in the blood and urine. When blood or milk determinations are made, a protein-free filtrate is used, but error is not appreciable when urinary protein is present. The estimations on milk agreed well with determinations made by the Munson Walker method.

RUTH TAYLOR.

BACTERIAL FILTERS. S. P. KRAMER, J. General Physiol. **9**:811, 1926.

In this preliminary note, the writer presents considerable evidence in favor of the view that filtrability is essentially a function of electrical charge, rather than of size of particle or of pores. Thus he found that substances, such as Victoria blue, which are held by a Berkefeld or other silicious filter, pass readily through a filter of plaster of Paris, which has a positive charge, while the silicious filters are negatively charged. Conversely, Congo red, which readily passes through the Berkefeld filter, is held by the plaster of Paris. A dilute solution of Congo red, made slightly acid, has its conditions of filtrability reversed. Filters made of calcined chemically pure calcium sulphate are neutral, as regards chemical charge, and with such filters both Victoria blue and Congo red pass through readily. Experiments with the so-called filtrable viruses showed that while they passed through the Berkefeld filters, they were retained uniformly by the plaster of Paris.

H. E. EGGERS

ULTRAFILTRATION THROUGH COLLODION MEMBRANES. ARTHUR GROLLMAN, J. General Physiol. **9**:813, 1926.

Grollman concludes that the view of collodion membranes acting as sieve-like bodies is adequate, if all factors are considered that might influence pore size. Facts which apparently are in contradiction to this hypothesis may be explained on the basis of a variable layer of absorbed fluid on the walls of the pores. Accordingly, it is unsafe to make deductions concerning the behavior of living membranes, from demonstration of changes produced in those of collodion. Similar effects in the two cases may be due to unrelated mechanisms.

H. E. EGGERS.

A STUDY OF THE LABORATORY AIDS TO THE DIAGNOSIS OF CHRONIC GONORRHEA IN WOMEN. R. S. PATTERSON, J. Immunol. **12**:293, 1926.

Patterson believes that a single satisfactory test is not available for the confirmation of the diagnosis of chronic gonorrhea in women. The pus-antigen

complement fixation reaction does give positive results in cases of gonorrhea in which the pus is rich in gonococci and, presumably, in antigenic substances; the reaction is specific, in that discharges from other infections did not give positive reactions; but in many chronic cases the discharges do not contain sufficient antigen to cause a reaction strong enough to be read with certainty. The pus-antigen complement fixation does not give as large a proportion of positive results in subacute and chronic cases as does the blood complement fixation reaction, and hence it is inferior to the latter as an aid to the diagnosis of chronic gonorrhea.

S. A. LEVINSON.

A COMPARATIVELY SIMPLE TECHNIC FOR THE BACTERIOLOGIC STUDY OF FECAL MATERIAL FOR CLINICAL AND EXPERIMENTAL PURPOSES. JOHN C. TORREY, J. Infect. Dis. **39**:351, 1926.

A group of three cultural procedures is described which collectively form the basis for as comprehensive a bacterial analysis of fecal material as may be desired except for certain specified purposes. This method has the advantage of requiring fewer types of mediums and fewer steps than those recommended heretofore for a similar purpose, and yet the resulting information is more definite and comprehensive.

The cultural elements of the technic include: brom-cresol purple, lactose agar plates, surface seeded and incubated aerobically; glucose blood agar plates incubated under conditions of reduced oxygen tension; and a series of cooked meat medium tubes with petrolatum caps to bring the anaerobic types to development. A standardized method for determining the virulence of members of the colon group is also described.

In the application of this technic to the examination of stool specimens certain points are emphasized.

A reaction more acid than P_H 6.2 or more alkaline than P_H 7.2 is indicative of abnormal bacterial conditions.

Microscopic examination of gram stained films prepared from stool specimens, except for certain specified purposes, is of little or no value.

An average count for viable *Bacillus coli* for adults is given and the possible significance of wide departures from this average as well as of unusually virulent colon strains in the intestine is discussed.

The possible relation of various types of streptococcus, such as *Streptococcus fecalis, Streptococcus salivarius, Streptococcus hemolyticus, Micrococcus zymogenes* and anaerobic types, to nonspecific ulcerative colitis and other chronic intestinal disorders, is considered in connection with the observations in a series of 132 persons. The rarity of *Streptococcus hemolyticus* in the large intestine is emphasized.

A tabulation is given illustrating the differential changes produced in cooked meat medium by the more noteworthy intestinal spore-bearing anaerobes and its use is suggested as a presumptive guide in fecal examinations.

The methods, as described, are adapted particularly to the study of material from the large intestine but with some obvious modifications and additions they may serve as a basis for a survey of the small intestine.

AUTHOR'S SUMMARY.

Society Transactions

PATHOLOGICAL SOCIETY OF PHILADELPHIA

Regular Meeting, Jan. 13, 1927

EUGENE L. OPIE, *Presiding*

A CASE OF AMEBIC APPENDICITIS WITH PERFORATION AND PERITONITIS. B. A. GOULEY.

This case was presented as being an unusual type of appendicitis and also because of the comparative rarity of this complication of amebic colitis, i. e., perforation and acute peritonitis.

The patient was a white man, aged 57, admitted to the University Hospital with general peritonitis. He died thirty-six hours later. The onset occurred ten days before death, with abdominal pain, fever and bloody diarrhea. Four days before death he had a hemorrhage by rectum.

Autopsy.—On opening the peritoneal cavity numerous fresh adhesions were noted nearly everywhere. The intestinal coils showed red streaks when pulled apart. A small amount of free fluid was present especially in the right iliac fossa. There were small collections of exudate in nearly all parts of the abdomen with hyperemia and a few small collections of pus. The appendix was found ruptured in the upper third and fluid was escaping; the upper third was black; the lower two thirds of the lumen was obliterated, and normal in color. The large intestine was extremely friable, rupturing on handling, and somewhat dark, especially the cecum and the ascending colon; it was greatly distended, chiefly with gas and some dark liquid. The small intestine was moderately distended; discoloration had not occurred.

Large intestine: The sigmoid presented numerous shallow elliptical ulcers, generally white. Approaching the cecum this appearance gave place to large patches of dark discoloration due apparently to hemorrhage. These patches became confluent with superficial ulceration and a few small blood clots. Evidence of fibrosis or of other chronic change was not seen. The process stopped sharply at the ileocecal valve.

Histology of the Appendix.—The section was from the junction of the cecum and the appendix, i. e., the upper third of the appendix. The wall was thickened by edema and necrotic change. Practically all of the mucosa was gangrenous, only a few of the tubules being partially stained. Most of this layer had sloughed away. The submucosa had become entirely necrosed and its borders were no longer definite. Occasionally in the mucosa, and more so in the submucosa round pale staining structures were noticed, larger than the large monocytes, and with a small, scarcely visible nucleus; many of them contained vacuoles. These were amebas (*Endomoeba histolytica*); their infiltration was best seen in the muscular layers. The inner layer had been practically lost in the destructive process. The amebas were also seen in the outer layer and out in the serosa, in the fibrinous exudate of acute peritonitis.

All of the blood vessels were congested. Amebas were found within some of the larger vessels; many lymphatics were crowded with them. Some of the larger vessels were thrombosed. Leukocytic infiltration was not present even in the acute peritoneal exudate.

TUBEROUS SCLEROSIS WITH RHABDOMYOMA OF HEART AND RENAL MALFORMATIONS. MORTON MCCUTCHEON.

Tuberous sclerosis is a condition of the brain characterized clinically by idiocy and epilepsy, and pathologically by sclerotic nodes of the cerebral cortex and subependymal tumors. The condition is believed to be congenital.

Such persons frequently die in childhood, few of them surviving longer than to early adult life.

It is extremely interesting and has long been known that with tuberous sclerosis are frequently associated peculiar lesions of the heart, kidneys and skin. It is especially with the heart and kidneys that I am concerned.

The first case was that of a white girl, aged 6 years, who died of inanition. At autopsy the brain presented the appearance typical of tuberous sclerosis. This brain was shown to the society by Dr. Freeman (*Arch. Neurol. & Psychiat.* **8**:614, 1922). Lesions were not found in the heart, but a special search was not made. Both kidneys presented numerous white nodules, varying in size from 4 mm. down to microscopic dimensions. On section they were found to be well defined from the surrounding normal renal tissue, though not encapsulated. They consisted of peculiar abnormally large fat cells, of numerous thick walled blood vessels and of masses of large undifferentiated round or columnar cells.

The second case was that of a female infant who died at the age of 1 year from inanition. There was the usual history of retarded mental development, and convulsions. The brain showed a single well defined area of gliosis, 1.5 cm. in diameter, situated in the right frontal lobe.

In sections of the heart was found an area, 2 mm. in length, which consisted of large spider-like cells, containing a huge vacuole. Some of these cells showed fairly definite cross striation, and were believed to be heart muscle cells of embryonal type.

In the kidneys, in a number of blocks of tissue, only a single abnormal area was located, consisting chiefly of hyperchromatic epithelial cells with only incomplete arrangement into tubules; among the latter lay numerous wide thin-walled vessels containing ghost corpuscles. The histologic picture of the kidney lesion, therefore, differed from that of the other case.

The chief point of interest in this presentation was the question which it suggested, what is the relation of lesions of the brain, the heart and the kidney, found in cases of tuberous sclerosis, to neoplasia? It is agreed by all authors that these lesions are due to developmental faults, but there is disagreement as to whether these various lesions are or are not true tumors. What is actually present is masses of embryonal tissue which have failed to differentiate, enclosed in normal tissue, and slowly growing along with the normal tissue. In the brain, such growth gives rise to serious disturbances, in the other organs, not. Sarcomatous change has been reported in the kidney nodules, but how frequently this happens is a matter of dispute. Metastasis has been reported in at least one case.

Cohnheim's theory of neoplasia derives tumors from persistent embryonal anlages. What support is lent to this theory by study of tuberous sclerosis? In my opinion, such study suggests that certain endogenous tumors of the brain, rhabdomyomas of the heart, and mixed tumors of the kidney may in fact arise from embryonal anlages, but it does not lend support to the view that the common and important varieties of cancer and sarcoma arise in such a way.

A Case of Rupture of the Heart. George M. Robson.

A white man, aged 75, was admitted to the service of Dr. A. Stengel at the University Hospital with symptoms leading to a diagnosis of cerebral thrombosis and softening, with general arteriosclerosis. For five days there was little change in his condition; then, suddenly, after a few gasping breaths, he died.

At autopsy the clinical diagnoses were confirmed. In addition, the pericardial sac contained about 300 cc. of blood clots and an equal amount of fluid blood. The hemorrhage was found to have occurred from a rupture on the anterior surface of the left ventricle. The rupture was 3 mm. in length, and a probe could be passed through it into the ventricle. The anterior coronary artery was sclerotic, and at a point probably corresponding to the origin of a branch supplying the ruptured area there was a red adherent thrombus, 5 mm. long.

This case of spontaneous rupture of the heart is typical in the age of the patient, in the clinical history and in pathologic changes.

MINNESOTA PATHOLOGICAL SOCIETY

George E. Fahr, M.D., *President*

E. T. Bell, M.D., *Secretary*

Jan. 19, 1927

Growth of the Thymus and Its Relation to Status Thymico-Lymphaticus and Thymic Symptoms. Edith Boyd.

1. The thymus in the new-born child shows a temporary loss of weight which probably is concomitant with the normal loss of weight in the body.

2. The fetal type of thymus is broad; the infantile type, elongate. This change of form is produced in the first two weeks of life by the expansion of the lungs (Noback).

3. Thymic symptoms may be produced in the first year of life by mechanical pressure of a normal gland on mediastinal structures, especially the recurrent laryngeal nerve. Our records do not show any case in which pressure on the trachea by the thymus caused death.

4. The observations which Paltauf has described as those of status thymico-lymphaticus represent the normal thymus and lymphoid tissue of the well nourished child.

5. Failure to recognize accidental involution has caused the confusion regarding the weight of the thymus and the misconception, status thymicolymphaticus.

6. The average weight of the thymus found at necropsy in well nourished persons is 13 Gm. at birth, 20 Gm. at 6 months and 35 Gm. at 13 years.

7. The average weight of the thymus found at necropsy in poorly nourished persons is 8 Gm. at 2 weeks, 6 Gm. at 6 months and 13 Gm. at 13 years. In general, the fluctuations in the weight of the thymus at any age period are concomitant with the fluctuations of the weight of the body. Some illnesses, such as influenza, may affect the thymus before they affect the nutrition of the body.

8. The growth curve of the thymus in a well nourished person is the same type as that of the lymphoid tissue in general.

REPORT OF A CASE OF STENOSIS OF THE RIGHT PULMONARY ARTERY WITH RIGHT VENTRICULAR HYPERTOPHY. J. S. McCARTNEY, JR.

A man, aged 43, had suffered for about three months with slight shortness of breath on exertion, and a slight cough, without hoarseness. He went to work as usual the day before his death, but came home late one afternoon because he was sick. He called a physician, thinking that he had bronchitis, but he did not consider his condition serious.

During the night he was unable to lie down because of dyspnea. In the morning he again called the physician. When seen the patient was apparently in a serious condition. He had marked cyanosis, dyspnea and signs of pulmonary edema. He was given morphine and atropine, and a little later an injection of strophanthin. He died a few minutes later, retaining consciousness almost to the end.

At necropsy, syphilitic aortitis was present with multiple aneurysms of the arch of the aorta, one 5 cm. in diameter, the others up to 2 cm. in diameter. The largest aneurysm projected anteriorly and to the left from the root of the aorta. The pulmonary ring was 8 cm. in circumference. The pulmonary artery measured 7 cm. in circumference 2 cm. above the valve. The mouths of both pulmonary arteries measured 4 cm. in circumference. The right pulmonary artery suddenly and rapidly became narrowed, 1 cm. from its beginning, and its lumen was reduced to a circumference of 1 cm. The narrowing, which was due to an apposition of opposing walls with the formation of adhesions between the portions in apposition, extended for a distance of 2.5 cm., when the artery again rapidly assumed a circumference of 2.5 cm. As seen on cross-section, the artery had somewhat the shape of a tennis racquet, the handle of the racquet representing the parts of the wall which were adherent to one another. The narrowed area was on the side toward the crotch between the right and left pulmonary arteries. On careful examination, it was seen that the large aneurysm previously mentioned lay immediately over this area of the narrowing of the right pulmonary artery. In the beginning of the right pulmonary artery was a protruding nodule 5 mm. in diameter.

The right ventricular wall measured from 5 mm. to 1 cm. in thickness — a definite hypertrophy. The cavity was moderately dilated. The lungs showed widespread congestion and edema; the liver, spleen and kidneys showed acute passive congestion, and a marked edema was present in the brain.

The case is unusual in that the stenosis of one pulmonary artery caused hypertrophy of the right ventricle.

Book Reviews

MESENTERIC VASCULAR OCCLUSION, SUPPLEMENTED BY AN APPENDIX OF SEVENTY-SIX ORIGINAL CASES. By A. J. COKKINIS, M.D., B.S., London, F.R.C.S., English Surgical Registrar London Lock Hospital. Pp. 159. New York, William Wood & Co., 1926.

The records of the London Hospital since 1900, inclusive, furnished sixty-two of the seventy-six "original cases" on which this monograph is based. Of the remainder, six are from Guy's Hospital and eight from observations by the author and his colleagues. Two of the seventy-six patients died without operation (no necropsy). One patient recovered without operation. The conditions in six others were determined at operation. Of these five recovered and one, who had cancer, was lost sight of. In twelve who died, examination was made solely at the time of operation; in twenty-seven others at both operation and necropsy, and in twenty-eight at necropsy alone.

In one of the best reviews of this subject, Embolism and Thrombosis of the Mesenteric Vessels by L. B. C. Trotter, 1913, there is a summary of 359 cases, and of these thirty were from the London Hospital. It is of some interest that Cokkinis found ten of these "not, strictly speaking, examples of mesenteric occlusion." The remaining twenty he also has used.

Thrombosis of the mesenteric veins is much more frequent than is obstruction of the arteries by either thrombosis or embolism. The former is represented by fifty-seven, the latter by nineteen of the seventy-six cases of this monograph. Of the nineteen arterial occlusions, all in the superior mesenteric, only two were due to autochthonous thrombosis and seventeen to embolism. One venous occlusion was old; the upper 7 cm. of the superior mesenteric vein and its ileocolic branch were completely obliterated and converted into a fibrous cord. One wishes for more details of the disease in this case. In three other bodies the superior mesenteric vein was occluded, the portal vein was normal and disease was not present in the districts drained by the veins. Thrombosis of the mesenteric veins was retrograde from the portal vein in twenty-two cases, it was secondary to infection in the peripheral parts drained in eighteen, and its cause in thirteen was not ascertained. Thrombosis of the inferior mesenteric vein was uncommon.

There is a great difference between venous and arterial obstruction of the mesenteric vessels. Since the first is never abrupt, a collateral circulation may develop. With complete closure of the superior or inferior mesenteric veins, or of even the portal vein, a compensatory venous drainage adequate in varying degrees may persist for years. It is only when the thrombosis in the larger venous trunks extends peripherally to the smallest venous arcades and straight veins which directly drain the bowel, that infarction with extensive necrosis occurs. If occlusion of the superior mesenteric artery comes on slowly, a compensatory arterial supply of blood to the bowel may develop through anastomosing branches of the gastroduodenal, internal iliac, lowermost intercostal and lumbar arteries. Anastomoses of the mesenteric veins are more extensive and more competent. Occasionally anomalous large venous or arterial anastomosing vessels are found.

Rough sketches of the results of experimental injection of the mesenteric vessels of human bodies, mainly the veins, with a good account of what was

learned by such studies occupy the first seventeen pages. The appendix has sixty-one pages. Difficulty in obtaining the special license required in England to keep animals alive after operation, prevented the animal experiments originally planned.

There is a gratifying increase in the frequency with which obstruction of the mesenteric blood vessels is recognized, but obstruction of these blood vessels is still chiefly studied at postmortem examinations. Highly competent surgeons operating early and successfully resecting large segments of necrotic bowel sometimes do not suspect the real cause of the gangrene. In many of the seventy-six cases, the clinical records of which are summarized in the appendix, diagnosis was not made; in many others the diagnosis was incorrect. Both surgeons and physicians may profitably study these records as well as what is presented elsewhere in this small carefully written volume.

A Statistical Survey of Three Thousand Autopsies from the Department of Pathology of the Stanford University Medical School. By William Ophüls, M.D., Stanford University, Calif. Stanford University Press, 1926. (Stanford University Publ., Univ. Ser., Medical Sciences, Vol I, No. 3, pp. 127-370).

Dr. Ophüls has performed a useful service to pathology in general in making available to other workers a general conspectus of the observations in this long series of necropsies, a considerable portion of which he has performed personally. In recent years, especially in the United States, it has seemed to be somewhat the fashion for pathologists either not to have, or to profess not to have, any interest in the statistical aspects of their labors. It seems reasonable to hope that Dr. Ophüls' monograph will have some influence in changing this unfortunate fashion. For obviously there are many aspects of diagnosis, prognosis and curative and preventive medicine which can be materially illuminated by sound statistical study of the results of routine necropsy examinations.

The plan of the book is as follows: There are, first, three introductory chapters dealing successively with (*a*) the character of the material in respect to social status and race; (*b*) the age distribution of the material as a whole; and (*c*) the relative frequency of various diseases or abnormalities. Then follow chapters dealing in detail with various pathologic conditions as follows: Tuberculosis; amyloid disease; septic infections; various infections; animal parasites; venereal diseases; arteriosclerosis and nephritis; thrombosis of heart and veins; cirrhosis, hematogenous pigmentation, and anemia; alcoholism and drug addiction; diseases of metabolism and endocrinopathies; concretions; congenital malformations; tumors; injuries and poisonings; miscellaneous conditions. The book ends with a detailed index. It is illustrated with sixteen charts, which have been much too severely reduced in the reproducing to make them easy to read. In fact some of them are so difficult to disentangle as largely to destroy their usefulness.

Since the book is essentially a painstaking record of detailed observations, without any attempt at broad generalization, it is impossible in the space of a review to make any comprehensive exposition of what the results of the study were. The original must be consulted for that. Except in the case of tuberculosis there is little attempt to compare the results in this series of necropsies with what has been brought to light in series of similar magnitude elsewhere. Nor is there a single reference to the biometric work which has been done on

necropsy material in England and in this country. Whether the author is ignorant of this work, or regards it as being without significance does not appear.

From the purely pathologic point of view the book is replete with interest. The chapters on tuberculosis, septic infections and arteriosclerosis and nephritis are perhaps the most interesting. In the first mentioned there is an analysis of the age incidence of tuberculous lesions which leads to the following results: "With increasing age the frequency of tuberculous lesions in the lungs (all forms included) increases fairly constantly, but the rise in frequency of incidence becomes quite slow after 50 years of age. . . . Active pulmonary tuberculosis is most common between 20 and 40, much less so later in life. The acute cases therefore are relatively common in young individuals and quite rare at ages above 40. . . . The subacute cases rise rapidly from 2 per cent in the first decade to over 20 per cent at ages between 20 and 40. From there on, their number decreases to 1 per cent at ages above 70. As the acute and subacute cases decrease, the chronic cases become relatively more numerous until at ages above 70 one finds chronic cases almost exclusively. . . . So far as the characteristic healed lesions at the apices are concerned, there is an actual increase with advancing age, or expressed in other words: infection of the apices occurs most commonly, no doubt, in early youth but continues to occur at later ages. The number of such infections which tend to heal probably also increase with advancing age. This conclusion coincides well with the general impression that in man the resistance to tuberculosis increases with advancing age."

It is needless to say that the pathologic opinions and judgments expressed in this book are shrewd and soundly grounded. In this aspect of the dual rôle which the author necessarily has had to play in this research, he is thoroughly expert and at home. From the technical statistical point of view it is difficult to find much to praise in the book. The fundamental difficulty is that the author obviously has had no special statistical training. There is practically no attempt whatever at any penetrating statistical analysis of the data, such as would inevitably be undertaken by an expert in this field. Essentially, all that Dr. Ophüls attempts anywhere to do is to set down the absolute and percentage frequencies of the various conditions discussed. Even within this modest sphere of statistical effort the work is open to criticism at various points. He fails in many places to make clear the basis from which particular percentages are computed, with the result that the reader who wishes to use the material later for comparative and synthetic discussion is bound to be greatly puzzled, if not unintentionally and (on his part)) unconsciously misled. Furthermore, except in a few instances, the attempt is not made to give detailed figures as to sex and age for the separate pathologic conditions discussed, which is again unfortunate for future users of this book. For example, opening the book at random, it is stated on page 286 that "marked hematogenous pigmentation was observed in 278 cases." But what was the age and sex of these 278 persons? Perhaps Dr. Ophüls would answer that it does not matter. Perhaps it does not, to him. But surely some future student is going to wish that the information were available. And the lack of such information will be still more keenly felt in reference to other lesions, more interesting and important than hematogenous pigmentation. If the author had called to his aid for the mere tabulation of his records the Division of Vital Statistics of the Census Bureau or the corresponding division of the California State Board of Health his intrinsically valuable records would have been tabulated in such a way as to be vastly more useful to future students. The somewhat contemptuous attitude of the pathologist toward the official vital statistician, which rather widely prevails, is only justified

in respect of one point. The vital statistician is forced to recognize and tabulate causes of death which are simply ridiculous, from the pathologist's point of view and in fact, if considered as accurate scientific records. But with about equal justice the vital statistician regards the pathologist's attempts at statistical tabulation and treatment of his much more accurate data, as too sad even to be funny. One cannot say which is the greater sinner.

PATHOLOGISCH-ANATOMISCHE DIAGNOSTIK AN DER LEICHE NEBST ANLEITUNG ZUM SEZIEREN. By HERMANN BEITZKE, O.Ö., Professor der pathologischen Anatomie an der Universität Graz. Pp. XI and 467, with 287 illustrations. Price, 37.80 marks. Münich: Verlag von J. F. Bergmann, 1926.

Beitzke's book was written to replace the "Pathologisch-anatomische Diagnostik" of Orth, his teacher, which has not been revised since the author's death. The preface states that the volume is not a textbook, but a guide to the gross pathologic anatomy of the necropsy. It is divided into an eleven page introduction, a 393 page general part and a forty-three page special part. The introduction pertains to the generalities of postmortem examination and, because of its elementary character, predisposes the reader against what is to follow. This impression is quickly dispelled, however, by the general part, the essential portion of the book, which is subdivided into thirty-seven sections, each of which is devoted to a particular region or organ of the body or to the postmortem examination of the infant. Each section is opened by a paragraph in italics describing the technic applicable to the region or organ under discussion. The Prussian regulations for medicolegal necropsies are followed, but methods other than the prescribed ones are also given whenever the author believes the modification is better. The paragraph on technic is followed by a short description in small type of the normal appearance and relations of the part or organ. Then follows a terse and inclusive discussion of the gross anatomic alterations which the organ may show.

Whereas the main general subdivision of the book is a taking apart of the body and a viewing of each part or organ as something unrelated to the whole, the final special part is in the nature of a putting together of observations which may be expected in certain disease processes. It deals with the interpretation of postmortem evidence in the light of the alterations which various diseases may produce. This material is divided into eight sections which take up in succession the blood diseases, the infectious diseases, general metabolic disturbances, intoxications, asphyxiation, death due to electricity, death due to heat or cold and death due to starvation. Pathologists will appreciate the brief final section which discusses cases in which the cause or mode of death remains unclear even after complete and careful postmortem examination. The subject matter of these various topics is of necessity brief, but the essential observations are given, and the completeness and newness of the discussion is attested by such headings as agranulocytosis, under the blood diseases, and mustard gas and phosgene, under the intoxications.

The criticism frequently made against German books, that of an inadequate index, does not apply to this volume. Aleukocytosis is listed as such and again with angina, under which there are nine entries. The young pathologist, who does not know the fetal age at which the pupillary membrane disappears or who may be unfamiliar with the technic of examining the eye for the presence of the membrane, will find Pupillarmembran in the index. In the text, rickets is spoken of as the English disease and as rachitis; both terms are given in the index. The partisan of a particular designation for scurvy

will find Skorbut, Barlowsche Krankheit and Möller-Barlowsche Krankheit. Although eponymic terminology is one of the banes of medical literature, it is a satisfaction to find in an index such terms as Buhl's Disease, Perthes' Disease and Wilson's Disease, especially when they relate to conditions which cannot well be concisely named by a single word.

The illustrations, of which there are 287, are in part from photographs, but chiefly from drawings. Forty-five of them are colored, some being in full color, the rest making use of the new German process which adds a single color—in this book usually light yellow—to black and white. All the illustrations are printed directly on the text page. On the whole they have been well chosen; the drawings depict gross lesions much better than do photographs.

Beginning with the feeling that the volume would be merely an elementary rehash of what every pathologist might be supposed to know, the reviewer lays it aside with the conviction that it contains, in comparatively brief space, a store of information greater than most American pathologists will be able to develop from their own experience in postmortem examination. To the young pathologist, who may feel that he needs a German text to keep himself familiar with the language, the book is recommended, not only because of the information which it contains but also because of the succinct German by means of which that information is imparted. To him who is only occasionally called on to perform a necropsy, especially one which may have medicolegal bearing, the book will be very helpful.

LOCAL IMMUNIZATION. SPECIFIC DRESSINGS. By A. BESREDKA. Translated by HARRY PLOTZ, M.D. Pp. 181. Price, $3.50. Baltimore: Williams & Wilkins Company, 1927.

This volume consists of a series of studies, published in French medical journals under the title "Pansements Spécifiques; études sur l'immunité locale," which in this English translation are admirably compiled and are far from being a mere vehicle for the publication of the author's experimental work on local immunity. The new concept of localized cellular immunity not dependent on the obligatory participation of antibodies is at once provocative and stimulates interest in the subjects under discussion.

In the first chapter Besredka explains the selective affinity that certain receptive cells in the skin possess for the virus in anthrax vaccination. Local immunity conferred by cutaneous vaccination, he says, carries with it an immunity which is not wholly localized, but which extends to the entire organism. This is not the case when the virus is injected intraperitoneally, intrapleurally or intravenously, since by these routes the animal is not rendered immune to anthrax. But once the skin is vaccinated, the localized immunity becomes a generalized state of immunity against the ingress of the anthrax virus, although cutaneous vaccination of this kind is not followed by production of antibodies. The author has well chosen anthrax as the type which best illustrates his new concept of local immunity.

The second chapter deals with local immunity to staphylococcus and streptococcus infections. The fact is emphasized that cutaneous inoculation is the basis of most infections caused by staphylococci and streptococci and that these two organisms have a selective affinity for receptive cells in the skin. Filtrates from killed broth cultures of staphylococci and streptococci applied in wet dressings to the infected tissues, he says, produce an immediate influx of leukocytes and a rapid disappearance of the pathogenic agent, and facilitate the elimination of cellular elements which retard cicatrization. Clinical results

with local application of such dressings — and in this chapter the translator deviates from the original text by substituting and adding new cases, with the approval of the author — are excellent. This new principle of applying the vaccine directly to the receptive tissues, he states, induces local immunity without the necessity for production of humoral antibodies. It is inferred that the inefficiency of subcutaneous vaccination with staphylococci and streptococci is due to the wrong way of application.

The third and fourth chapters are devoted to oral immunization in dysentery and typhoid fever, which in the hands of the French clinicians has produced striking results. In chapter 4 one is struck with the fact that Besredka presents few experiments with the typhoid bacillus, and that most of his conclusions are based on experiments with paratyphoid B antigens. To make his position in regard to specific local immunity in typhoid fevers tenable, a more extensive elaboration of vaccination with *Bacillus typhosus* is desirable.

The final chapter deals extensively with theories concerning local and general immunity. It is evident that the author endeavors to meet contradictions in various old concepts of local and general immunity by introducing his new concept of the receptive cells in single organs, such as the skin in anthrax, staphylococcus and streptococcus infections, and the intestines in dysentery and typhoid infections as a fourth factor in immunization, supplementing the triad of virus, phagocytes and antibodies. Besredka's conception of local immunity by means of vaccines as a process of desensitization of the receptive cells in the skin or the intestines by direct contact between these cells and the virus is a stimulating idea formulated from analogy with anaphylaxis. Since the bacterial cells themselves are coagulated by heat or chemicals, it remains for the soluble derivative of the bacterial cell to enter into reaction with the receptive cells, by dulling their sensitiveness to the antigen or, in other words, immunizing them. Liberation of this derivative is accomplished by leukocytic disintegration and digestion of the bacterial cells, which under ordinary conditions takes place about four or five days after the injection of the antigen. The free phagocytes in the blood render the vaccine assimilable for the receptive cells in the skin or in the intestines. Vaccination of the receptive cells, he says, is subsequently brought about. The process of liberating is readily reduced in time, even to twenty-four hours, by producing in vitro what the phagocytes accomplish in vivo, by means of injecting filtered cultures. There are undeniable shortcomings in the final chapter, in particular when the author states that the toxic substance contained in the streptococcus is unable to produce antibodies. In view of the recent work in scarlet fever and erysipelas therapy with true streptococcic antitoxins, the author's present position should be revised.

The book is ably translated, contains an extensive bibliography and is worthily printed. This small volume constitutes an absorbing record of broad laboratory experience and should appeal both to the immunologist and to all who are interested in medical theory and practice.

GRUNDRISS DER PATHOLOGISCHEN ANATOMIE. VON PROF. DR. GOTTHOLD HERXHEIMER, Prosektor am städtischen Krankenhaus zu Wiesbaden. Allgemeiner Teil. Ed. 19 of Schmaus' Grundriss der Pathologischen Anatomie. Paper. Price, 28.80 marks. Pp. 312, with 466, mostly colored, illustrations. Munich: J. F. Bergmann, 1927.

Those who are familiar with the earlier editions of Schmaus' book, the sixth of which was translated into English by A. E. Thayer (edited by James Ewing)

in 1902, will hardly recognize the present volume. Herxheimer, who has been revising this popular German textbook since its eighth edition, has lately been offering a thoroughly reconstructed product. For economic reasons, the last two editions had to be abbreviated considerably, but the present issue has been allowed normal size and expansion. The volume under consideration is not independent; it is only a separately bound part of the whole book, the part dealing with general pathologic anatomy, with a table of contents but no index.

The introduction includes a discussion of current pathologic terms, a good description of the signs of death and postmortal phenomena and, for the scope of the book, a rather lengthy discourse on the cell, along general biologic principles, not including morphology. The subject-matter is arranged much in the manner found in other textbooks. It consists of nine chapters on the usual topics, of which five are devoted to general pathologic anatomy of the tissues and four to causes of disease. The contents of the chapters are methodically arranged, though most of the headings are cumbersome. The book is well balanced and includes the latest ideas on the various subjects. This is especially apparent in such topics as tuberculosis, infections, immunity, experimental tumor production and a few others which have been entirely rewritten for the present edition. Indeed, it seems that the aim of the author was not so much to present to the student a judicially selected material as to make the book as complete and compact as possible. This he has accomplished. The pages are large (imp. octavo), the print is small and approximately one third of the volume is in fine print. The style is rather cramped and mostly unengaging. The illustrations, however, are excellent and accompanied by good legends.

Altogether the book does not show any new departures. It is a typical, modern German textbook on a small scale, built on traditional lines, with the main emphasis on pathologic anatomy. Excepting perhaps McCallum's Pathology, it differs little essentially from modern American textbooks. Only the name is different. Instead of "pathological anatomy" American textbooks use the broad term "pathology," which, of course, includes the study of disease from any angle. However, "pathological anatomy," if not awkward, is slightly ambiguous. This is felt by the Germans also, and they often try to obviate it by writing the adjective with a capital letter. To the American student who is familiar with the German language the book may be recommended for a brief survey of many important topics in general pathology. Unfortunately it does not include any references to the literature.

HUMAN PATHOLOGY. A TEXTBOOK. By HOWARD T. KARSNER, M.D., Professor of Pathology, School of Medicine, Western Reserve University, Cleveland. With an introduction by SIMON FLEXNER, M.D. Price, $10. Pp. 980 with 20 illustrations in color and 443 black and white. Philadelphia and London: J. B. Lippincott Company, 1926.

In his preface, the author states that "the purpose of this book is to present the morphological alterations incident to disease, in the light of modern views as to their functional significance," and this object governs the presentation generally. The book is divided into general and systemic pathologic anatomy. It covers the major portions of pathologic anatomy in a thoroughly satisfactory manner. The descriptions are clear and comprehensive. In future editions chapters on microbic etiology and on immunology should be added, in order to give a more complete picture of fundamental pathologic processes. In discussing the nonsuppurative diseases, the terminology of Volhard and Fahr (nephrosis, nephritis and nephrosclerosis) is followed with advantage for the

student. The various granulomatous processes are described with considerable detail, but certain acute infectious diseases, injuries due to physical agents and the larger animal parasites are not considered.

There is room for improvement of the index. The illustrations are almost without exception interesting and instructive. Ample directions to original articles are given through lists of references at the end of the chapters; most of the references are to articles in English published in the course of the last six years. The book can serve usefully as an introductory or supplementary guide to the study of pathologic morphology and its bearing on functional disturbances of clinical interest, but it is not intended to be complete enough to answer satisfactorily the requirements placed on a work of reference.

Books Received

Beiträge zur Kenntnis der Genese der Ovarial Embryome. Experimentelle Untersuchungen über Parthenogenetische Ovarialgravidität bei Amphibien. Aus dem Pathologischen Institut der Universität Uppsala Akademische Abhandlung von Wilhelm Bosaeus. Mit 31 tafeln, pp. 301. Uppsala: Almquist & Wiksells, 1926.

A Textbook of Bacteriology. A Treatise on the Application of Bacteriology and Immunology to the Etiology, Diagnosis, Specific Therapy and Prevention of Infectious Diseases for Students and Practitioners of Medicine and Public Health. By Hans Zinsser, M.D., Professor of Bacteriology and Immunology, Harvard University Medical School. With a Section on Pathogenic Protozoa by E. E. Tysser, A.M., M.D., Professor of Comparative Pathology, Harvard University Medical School. Rewritten, revised and reset. Ed. 6. With 181 illustrations in the text. Pp. 1,053. New York—London: D. Appleton & Co., 1927.

The Natural Processes of Healing in Pulmonary Tuberculosis. By Marc Jaquerod, M.D., Physician in Charge, Grand-Hotel Sanatorium Leysin Switzerland, Medical Director of the "Societe Climaterique de Leysin." Translated by J. Denny Sinclair. With 60 X-ray illustrations and 45 diagrams. Pp. 107. New York: William Wood & Co., 1927.

Studies on Tsutsugamushi Disease (Japanese Flood Fever). By Rinya Kawamura, M.D., Professor of Pathology, Niigata Medical College, Miigata Japan. Published as special nos. 1 and 2, vol. IV of The Medical Bulletin, College of Medicine, University of Cincinnati. Pp. 229, 25 plates. English translation, edited by N. C. Foot and Shiro Tashiro, 1926.

Preventive Medicine and Hygiene. By Milton J. Rosenau, Professor of Preventive Medicine and Hygiene, Harvard Medical School. With chapters on Mental Hygiene by Abraham Myerson; Sewage and Garbage, by Gordon M. Fair; Vital Statistics, by John W. Trask; Statistical Methods, by Carl R. Doering; Conservation of Vision, by J. Herbert Waite. Ed. 5. Pp. 1,458. New York—London: D. Appleton & Co., 1927.

Forensic Medicine. Illustrated by Photographs and Descriptive Cases. By Harvey Littlejohn, M.A., M.B., B.Sc., F.R.C.S.Ed., F.R.S.E., Ragius Professor of Forensic Medicine, University of Edinburgh. With 183 illustrations. London: J. & A. Churchill, 1925.

Textbook of Biological Chemistry. By James B. Sumner, Ph.D., Assistant Professor of Biological Chemistry, Cornell University. Price, $3.50. Pp. 283. New York: The Macmillan Company.

Pathologisch-Anatomische Diagnostik an der Leiche Nebst Anleitung zum Sezieren. Von Dr. Hermann Beitzke, O. Ö. Professor der Pathologischen Anatomie an der Universitat Graz. Mit 287 Teilweise-Farbigen Abbildungen. Price, 36 marks (37.80, bound). Pp. 467. Munich: J. F. Bergmann, 1926.

THE HUMAN CEREBROSPINAL FLUID. Association for Research in Nervous and Mental Disease. A Series of Research Publications. Vol. IV. New York: Paul B. Hoeber, 1924.

PHYSIOLOGY AND BIOCHEMISTRY IN MODERN MEDICINE. By J. J. R. Macleod, Professor of Physiology, University of Toronto. Assisted by Roy G. Pearce, A. C. Redfield, N. B. Taylor, J. M. D. Olmsted and others. Ed. 5. With 291 illustrations, including 9 plates in color. Price, $11. St. Louis: C. V. Mosby Company, 1926.

REPORT OF THE MEDICAL RESEARCH COUNCIL FOR THE YEAR 1925-1926. Pp. 161. Price, 3s. 6d., net. London: His Majesty's Stationary Office, 1926.

RESEARCHES ON HOOKWORM IN CHINA. By W. W. Cort, J. B. Grant, N. R. Stoll and others. Pp. 398. Price, $3.50. Am. J. Hygiene, Monographic series no. 7, 1926.

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